THE SOCIAL INSTITUTION OF CLINICAL RESEARCH INVOLVING HUMAN SUBJECTS: A CONCEPTUAL AND ETHICAL ANALYSIS

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This thesis assesses clinical research involving human subjects as a social institution of global reach. Scientific, philosophical, and cultural dimensions of clinical research are examined for their contributions to the construction of trials, and two philosophical interpretations of scientific methodology are consulted for their views about the penetration of scientific theories by social values: Hugh Lacey’s positive empiricist account of the role of cognitive values and social strategies in science, and Helen Longino’s contextualist feminist theory of scientific inquiry, objectivity, and social knowledge. The socio-cultural construction of the conceptual and ethical structure of clinical research is emphasized. Ethical analyses of clinical research focus on the use of divergent normative standards for clinical trials in the developed and developing world. The dominant bioethical model offered for transcultural ethical research, principlism, is described and critically assessed. The transnational ACTG 076 clinical trials are presented as a case study of global research and bioethical evaluation. Martha Nussbaum’s human capabilities model is proposed as an alternative, contextualist framework of clinical research ethics for its particular focus on the ethics and politics of distributive justice, which is a crucial issue in the contexts of health care and clinical research.
For Neocles
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FOREWORD

Any reference to clinical research involving human subjects brings to mind the idea of a scientific project leading to medical and pharmaceutical outcomes. The present thesis is premised on the alternative idea that clinical research is principally a social institution, whose scope has been expanded globally. This conceptualization emerges from the multitude of social interactions and practices that form the structures and functions of clinical research, and whose historical persistence points to past and anticipated future contributions of research in alleviating disease.

In this thesis, the conceptualization of clinical research as a social institution is grounded in a descriptive macroscopic account of several aspects of research that exemplify its social character. I have charted the array of groups, organizations, and institutions engaged in the research enterprise. I have also highlighted important ethical issues related to research misconduct in the history of medicine, and the resulting public policy rules for the protection of patient-subjects.

Particular attention is paid to transnational clinical trials and the socio-economic parameters forming the background of research sites in developing countries. These parameters, which include major health crises such as the AIDS epidemic, have increased the volume of Western-sponsored clinical research hosted in the Third world, and especially the testing of therapies that are of interest to Western consumers. This thesis emphasizes the fact that much in the way of health care available to Third world citizens is distributed through clinical trials, and interrogates the differential ethical standards in research conducted in developed and developing countries.
A microscopic examination is then conducted of the nature of beliefs entering the conceptual structure of clinical research. Understanding this structure, and the values that support it, is essential to understanding the values of the ethics of clinical research. This analysis probes notions of health, disease, and human wellbeing/body from a cultural perspective of race, gender, and sexuality. Egalitarian and libertarian theories of distributive justice in health care reveal socio-economic meanings of health and disease. In the context of medical technology, issues related to managing the processes of disease, death, and transplantation bring out important social, moral, and legal meanings of the human body. In the same context, the methodologies of randomized clinical trials are also explained.

To examine the nature of scientific beliefs entering the conceptual structure of clinical research, my analysis considers Hugh Lacey’s positivist empiricist account of the role of cognitive and non-cognitive values in the production of scientific knowledge, and Helen Longino’s contextualist feminist theory of scientific inquiry. Both accounts argue for the penetration and shaping of scientific theories (beliefs) by social values, consistent with the findings in the rest of the analysis.

The socio-cultural construction and mutability of clinical research concepts warrants alternative models for the ethical theorization and assessment of clinical trials, and may challenge the dominant bioethical, four-principle framework, which the thesis explicates and critically assesses. The sub-Saharan ACTG 076 clinical trials, testing the efficacy of a therapy in preventing HIV vertical transmission, are presented as a study case of global research and bioethical assessment. Ethical problems arising in these trials are discussed, and the issue of justice in transnational research is particularly stressed.
A preliminary account of Martha Nussbaum’s human capabilities model is proposed as an alternative normative framework for the ethical assessment of transnational clinical research. This suggestion is based on the combination of two features of the model: its capacity to contextualize clinical trials within their socio-economic, political, and cultural circumstances, and its theoretical position on distributive justice, whose material conditions are defined in terms of basic human functioning. Because any discussion of clinical trials hosted in resource-poor countries has to include considerations of health care allocation, I argue that Nussbaum’s model offers a more comprehensive ethical assessment of (transnational) clinical research thanks to its focus on the politics and ethics of distributive justice.
CHAPTER 1  
MAPPING THE SOCIAL LANDSCAPE OF CLINICAL RESEARCH

The new therapies and the requirement of human experimentation

The dawn of the twenty-first century has unmistakably revealed the profound significance, and also the remarkable speed in the unfolding, of what seems to have been humanity’s foremost characteristic throughout its history: the inexorable human quest for self-modification. Indeed, human endeavor seems to have always been guided by the desire, and most certainly by the need, to rework, alter, and—whenever possible—rebuild anew the very human condition in its various forms, whether individual or societal, physical or abstracted. It is this desire for change (perhaps often unconscious but nonetheless powerful) that has made us develop science and technology as means to understand and control the natural world. The same urge, I believe, is what drives humanity to mold the social world into an astonishing diversity of structures and systems—from religious rituals to macro-economic strategies—that may generate new types of social living.

In the scientific arena, this exertion for “metamorphosis,” so to speak, has been exemplified chiefly by a turn-of-the-century biomedical revolution whose supreme accomplishment is the elucidation of the human genome sequence. Indeed, no scientific and technological achievement—except perhaps the informatics revolution of the twentieth century—can match the new one in the scope and depth of its anticipated medical outcomes, and the social implications it is bound to have on the quality of human life. This is so because the new biomedical technologies aim at no less than the recombination of human DNA, that is, the transfiguration of our genetic material. The idea behind this daring move is to create new
possibilities for the development of therapeutic strategies that may be—as we hope—in safety and efficacy. The ultimate goal is, thereby, the radical enhancement of human health, longevity, and even physical appearance.

Although this endeavor, generically termed human genomics, was ushered in with great caution and suspicion as a potential threat to what various ideologies take to be the essence of human nature (if one really exists), it has been heralded at the same time as the tool that can rid humankind of some of its most agonizing ailments (e.g. Parkinson’s or Alzheimer’s disease, diabetes, and liver or kidney failure). Genocentric technologies, such as pharmacogenetics, embryonic stem cell manipulation, and gene therapy, may be currently facing substantial technical impediments or ethical challenges, but they are expected to become crucial tools in the production of twenty-first-century therapies. In the new, hybrid context of clinical/molecular medicine, the already established medical practices will inevitably undergo structural adjustments, but will certainly continue to play an important part.

Among these practices, and one as old as medicine itself, is the process of human experimentation, which, in our days, is referred to as clinical research involving human subjects. Practiced all along the 2,000-year-long history of Western medicine in some form or other, clinical research has been established as a necessary device for the development of new diagnostic and therapeutic interventions in the struggle against disease.\(^2\)

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1 Tampering with the human physical and mental attributes (i.e. genetically-induced somatic pliability for specific ends—say, athletic pursuits—or neuro-pharmacologically-induced control of behavior—say, to manage depression) is perceived as a deterministic threat to human autonomy, which is assumed to be a key part of an imagined human nature. As a result, free society and polity, also seen as manifestations of human nature, are perceived as threatened. For a discussion of these emerging moral issues, see Fukuyama.

2 For a brief summary of the history of human experimentation, see Brieger 684-687.
Although often surrounded by an aura of ethical concern due to its very method of experimenting on the human body (which in some senses has been identified with the human “person”), clinical research has found sanction in the role it plays in generating knowledge necessary for restoring individual health, and thereby in preserving and enhancing public health and wellness. Therefore, it would not be out of place to see human experimentation as part of this relentless human effort toward self-modification, for it utilizes the human body as a vehicle for transforming individual and social destiny (to the extent that human destiny depends on “healthy” biological functioning).

In the emerging context of clinical/molecular medicine the practice of clinical research aimed at the development of innovative therapies, purported to be life-saving and/or life-enhancing, is bound to be decisive. For one thing, the new drug approach of pharmacogenetics, conceived as the customized design of drugs to accommodate individual patients’ specific genetic profiles as a way of minimizing drug side effects, will depend heavily on testing the new treatments on human subjects. The only difference from the conventional drug-testing mechanism will be the inclusion of patients who will not only be diagnosed as having the same disease of interest, but will also share a common basic genotype to which the drug under investigation will be tailored.

Another therapeutic concept that will require serious investment in clinical research is gene therapy, whose basic principle is the replacement of defective genes (that are thought to be the cause of disease) by “normal” (or “healthy”) ones that are anticipated to generate healthy phenotypes, and thereby restore health. This effort is currently concentrated on creating safer methods in delivering gene therapy to human subjects.
Finally, the most promising therapeutic concept (still under investigation) is that of utilizing *embryonic stem cells* to generate replacement cells, tissues, and organs that can avoid immuno-rejection. This procedure is currently the object of heated moral and political debate. However, once (if at all) moral matters surrounding stem cell research are resolved, efforts to develop this therapeutic approach will be amplified to include the testing of the safety and efficacy of this method through large-scale clinical trials. The impetus for advancing this research is driven by no less than an ever-increasing demand for transplants that can be genetically matched, and hence are safer and more effective.

**Social and ethical concerns about clinical research: the goals of this thesis**

We, therefore, see how clinical research is anticipated to make a significant contribution to the development of revolutionary therapies in the twenty-first century, and thus to human self-modification in an exciting new chapter of medicine’s history. Although the significance of research has primarily been viewed as deriving from what it can practically do for individual and public health, not everything is up for sacrifice in the name of medical progress. Human experimentation has historically raised ethical concerns among medical practitioners and researchers but, most importantly, within the broader society as well.

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3 The stem cells used by this technology are derived from embryos utilized for therapeutic, and not for reproductive, purposes. However, as each embryo has the potential to develop into a fetus, the debate principally centers on a faith-based claim that the embryo should be entitled to the moral and legal status of a person. The question then arises whether it is ethical to utilize these embryos merely as biological material for the extraction of stem cells and eventually have them perish. For a brief discussion of ethical concerns and misconceptions relevant to genomic-based technologies, and of some of their health care implications, see Feldbaum 975.
For instance, the old anti-vivisection movement,⁴ or public grievances about irresponsible and abusive clinical trials,⁵ manifest a kind of collective anxiety about clinical research, and a desire for closer ethical scrutiny for its procedures. Indeed, a normative approach to clinical research, from an ethical/philosophical viewpoint, has evolved through the years as part of the bioethics movement toward establishing biomedical practices that are morally acceptable.

This ethical approach to clinical research is mostly inspired by a concern for the individual patient, or research subject, and it is not always clear to what extent the social context of biomedical practices is taken into account. Given the multiple ways in which the social character of clinical studies is exemplified (and which I am about to consider), a social theorization of clinical research is both appropriate and necessary for a more rounded and contextualized critical assessment of its procedures, goals, and general ramifications. This would also be justified in view of the tremendous social impact that the experimental therapies we mentioned are anticipated to have, and which will require a high investment in clinical research for their eventual development.

This thesis is premised on the significance of such an alternative social assessment, and the rest of this chapter is an attempt to establish this significance by reviewing a variety of aspects of clinical research from a macroscopic social perspective. More specifically, this chapter intends to explore general structures and functions of human experimentation that underscore its significance for human health and wellbeing, and its character as a broad social institution that stretches across national borders and cultural venues.

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⁴ Atrocious though vivisection may be, it persisted well into the 19th century making use of humans, and is still practiced on animals to this day. For a brief reference to vivisectionism and social movements against it, see Brieger 684-7.

⁵ Lemonick and Goldstein 46-55
I will, therefore, present an overview of the scientific/technical, medical, economic, and political features of clinical research, as well as of the philosophical debates related to it. To underscore the global character of the institution of clinical research, some emphasis will be placed on the socio-economic issues of HIV/AIDS clinical trials conducted in developing countries, and how these affect the question of justice, which is central to clinical research. This overview can set the stage for the microscopic analysis of conceptual and ethical aspects of research that will follow in the next two chapters of the thesis.

The second chapter will analyze the conceptual basis of clinical research in an effort to show that notions, entering both commonly-held and scientific beliefs we come to hold about research, are socially- and culturally-constructed. In this part, I aim to underscore the social component embedded in scientific beliefs (that we may call “theories”) about medicine and clinical research. This component allows human value to shape the way we reflect about human experimentation, whether in designing research trials, evaluating their ethical status, or regulating them through appropriate guidelines.

In the third and final chapter, I shall review the conceptual structure of the dominant ethical framework used for examining the ethical merits of research (as well as the physician-patient relationship, generally speaking). In the context of biomedical ethical reflection, this framework is referred to as the *principlist bioethical model*, and is purported to be of universal value. To illustrate the ethical tribulations of clinical research, especially in its transnational version, I then proceed by giving an account of clinical trials, conducted (mostly) in sub-Saharan Africa, which involved HIV-positive pregnant women.

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6 Beauchamp and Childress (2001)
Addressing the moral conflicts posed by this research seems to have been beyond the analytical power of restricted bioethics, and more of an ethical and normative concern regarding the politics of Third world development. In seeking a better ethical response to global clinical research, I suggest examining Martha Nussbaum’s *human capabilities approach*, which proposes the constitutional adoption of a specific set of principles as minimal political goods. These principles refer to human capabilities/standards that can be used to assess degrees of individual human flourishing, social development, and distributive justice.

Because a full explication of this theory surpasses the scope of this thesis, my goal is to suggest this view as a good candidate theory for the ethical assessment of clinical research conducted in an environment of great social inequalities and abject poverty. Although not a bioethical—or even a complete—theory of justice, the strength of this framework is based on its ability to locate ethical considerations of justice in solid socio-cultural, political, and economic contexts, and thereby is applicable to the social institution of clinical research at both the local and global level.

The social import of clinical research

I have claimed that clinical research is an endeavor whose value and content can be studied in a social context. I will now proceed to examine the various features of research that manifest this social character. Thus, the foremost implication of this enterprise is that it engages a great number of people, and affects their lives in profound ways. Viewed in a broad social sense, the primary social outcome of human experimentation is closely connected with its *raison d’être*, that is, the relentless generation of fresh insight into the biology of disease. Typically,

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7 Nussbaum
the central objective of clinical research “is to develop generalizable knowledge to improve health and/or increase understanding of human biology.” Therefore, its social significance is primarily derived from its capacity to produce life-saving/enhancing therapies, and thereby to improve the health and life expectancy of millions of people.

Clinical research can also be viewed as a form of health care, in the context of which participant patient-subjects are provided with needed therapy, insofar as this is possible considering the research burdens, and risk to their (physical and/or psychological) wellbeing, that they must assume. Indeed, populations of patients suffering from ailments for which no established, or largely ineffective, therapies exist opt to enter clinical trials in the hope of gaining substantial therapeutic benefit from promising experimental regimens, the so-called novel therapies.

A dramatic blurring of the research/health care dividing line occurred in the late 1980s through the strong activism of the gay community, which was then being ravaged by AIDS. As people were desperately seeking any life-prolonging treatment, gay and other activists pushed for more federal funding that would allow increased HIV research, and regulations that would

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8 Generalizable knowledge is defined as consisting of “theories, principles, or relationships (or the accumulation of data on which they may be based) that can be corroborated by accepted scientific observation and inference.” Levine, R.J. 3 (1986)

9 Emanuel, E.J., D. Wendler, and C. Grady 2701

10 For more details on viewing clinical research as an opportunity for therapeutic benefit rather than a venture of risk, and respective claims of justice, see Powers 154-5.
facilitate people’s access to it as a way of receiving any treatment that held some promise at the
time.\textsuperscript{11}

The research-as-health-care approach may be incompatible with the main knowledge-
driven goal of clinical research, and this creates a tension with weighty consequences for
research subjects.\textsuperscript{12} Indeed, clinical research is not medical care strictly speaking, because the
latter refers to the practice of medicine, or behavioral therapy, based on the provision of
diagnostic and preventive, or curative, treatment. At the very least, however, participation in a
clinical study usually entails undergoing treatments that are necessary for the successful testing
of the research hypothesis, and may be significant for the subjects’ wellbeing irrespective of
research.

The disguise of research under the cloak of medical care is also reinforced by pervasive
social and economic conditions. Lack of funds required for the construction of necessary
medical infrastructure, and for the provision of needed drug therapies to patients, makes basic
health care unavailable to a disturbingly large number of people around the globe, especially in
developing countries. Even in a country as affluent as the United States, “thirty-nine to forty-
two million or so Americans [were] estimated by snapshot surveys to be uninsured at a specific
point in time during 2001,”\textsuperscript{13} and hence to lack meaningful medical care, because of the absence
of universal health coverage in the U.S.

\textsuperscript{11} The conservative Reagan administration at first kept silence about what resembled an epidemic
that only struck gays, thus evading a commitment to fund pertinent research. Specter 56-65;
Levine, C. 108 (1996); Monette

\textsuperscript{12} This tension is typically exemplified by cases of clinical trials “abruptly” terminated well
before their anticipated conclusion because the research hypotheses have been answered, thus
depriving subjects from a whole therapeutic benefit.

\textsuperscript{13} Reinhardt
Ironically, even those Americans who can afford to buy health insurance are not safeguarded from impoverishment due to illness. Massive debt to pay medical bills that insurance will not cover, and even foreclosure of vital assets, is a looming prospect for numerous middle-class families every year. Indeed, “nearly 1.5 million couples or individuals filed bankruptcy petitions in 2001, a 360 percent increase since 1980.” Meanwhile vast sums of insurance monies are funneled into the cost management, and remunerative assets for high administrators and shareholders, of various Health Management Organizations (HMOs). The resulting, and ever increasing, disparity in health care among the “haves” and the “have-nots” is often fulfilled by clinical research (although this is not gratuitous either and, in some cases, turns out to be quite costly), which makes for a proposition and practice with questionable ethical merits due to its embedded risk factor.

Clinical research as an individual and intersubjective experience

Viewed from the (narrower) perspective of the individual, clinical research brings together numerous persons of diverse intellectual, social, and cultural backgrounds, and through various associations (of which the one between the clinician-investigator and patient-subject is principal), it engages them in a multifaceted exchange rooted in the human capacities of reason, imagination, and moral understanding. A clinical research project may not be evaluated merely in terms of the production of scientific knowledge and eventual drug development, but also in light of the ways in which the lives of participant researchers, subjects, and members of affected communities are shaped.

Thus, the restoration of a patient’s health, or the hope for a life-saving remedy in the near future, energizes people with satisfaction and optimism. Conversely, clinical malpractice, or the

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14 Himmelstein et al.; Reinhardt
non-fulfillment of patients’ health care expectations in the context of research (whether or not justified, given that research is not health care, strictly speaking), brings about sentiments of dissatisfaction, bitterness, and even despair. Whatever their aspirations, capacities, and roles, persons partaking in trials shape the research experience, just as their lives (and even their conception of the “good life”), are shaped by it.

**The social character of clinical research rooted in philosophical thought**

Theorizing clinical research in a social framework is akin to its moral justification, which draws from specific views of society. As a medical practice with important social consequences, clinical research must be justified so as to be ethically acceptable to the scientific community (including research protocol reviewers), potential research subjects, and the general public. The legitimacy of justification is based on particular approaches to society offering philosophical (and often theological or religious) outlooks on human agency, the nature of society, and the meaning of morality. The various debates examining the functions and ethics of clinical research are in turn informed by these specific views, thus allowing the social context of human research to emerge.  

Hence, a utilitarian social and moral approach to clinical trials, viewing the individual as part of a social whole, and emphasizing the maximization of health benefit for the greatest number of people (even at the relative risk of a comparably small number of subjects), may justify increased free rein for clinical research. Conversely, a Christian or Kantian ethic, embracing the inviolability of the human person (set off against its broader social group and system), and upholding the moral obligation to treat one as an end and not only as a means, is bound to be more restrictive regarding the scope and practices of what it considers to be

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15 For a brief reference to the social theorization of clinical research, see Capron 692.
justifiable clinical research. Both approaches illustrate how clinical trials, with regard to their moral justification, can be placed in a social context and become a befitting subject matter of social investigation.

Social institutions of clinical research

Insofar as clinical research is conducted within social institutions and structures, and according to norms developed by ethical and professional bodies within them, it can be suitably analyzed in a social theoretical framework. Some institutional milieus generating, hosting, or supporting (financially and socially) clinical research are the medical profession, the pharmaceutical industry, the modern research hospital, institutions of higher learning, and governmental agencies (i.e. FDA, NIH, etc.), to name a few.

Within these institutions, research oversight groups are involved in assessing the particular tasks of the clinical trial process. Thus, so-called Institutional Review Boards (IRBs), or Institutional Ethical Committees (IECs), are professional bodies evaluating the compliance of proposed trials with international/federal rules and regulations for the conduct of clinical research, and the appropriateness of implementing trial protocols in specific clinical settings.

More specifically, an IRB—which, as a rule, provides the final say regarding research approval—takes a qualitative measure of the proposed research procedures and objectives in terms of their scientific, technical, and ethical soundness, against a specific set of research guidelines. These guidelines are used as a technical and ethical benchmark to define the kinds of

\[\text{\textsuperscript{16}} \text{Ibid.}\]

\[\text{\textsuperscript{17}} \text{Ibid.}\]

\[\text{\textsuperscript{18}} \text{This appellation is most commonly used in Canada, whereas “IRBs” is the usual designation for these committees in the U.S.A.}\]
protection (from undue research risk) that the proposed studies should offer their prospective research subjects. Trials are subsequently monitored by some external regulatory modality, such as oversight committees, which inspect the degree of research compliance with IRB-authorized rules by assessing the data and general quality of research in the course of a trial.\textsuperscript{19}

Of particular social interest for its worldwide impact on the management of personal and public health is the pharmaceutical enterprise sponsored by universities and medical schools, but predominantly by the drug industry. As an economic venture, the latter commands an enormous share of stakes across national and international economies, and has thereby gained the ability to exert the political influence that invariably accompanies economic power. Clinical trials are at the heart of success (or failure) of pharmaceutical projects, and their analysis in a social context is extremely significant for understanding the various power relationships that shape the environment of drug production and, consequently, of health care.

Clinical research policy

Clinical research does not merely contribute to the development of new drug therapies; it also influences public policy, and shapes the law in the area of health care, broadly speaking. Clinical trials often provide the scientific and social field whereby new biomedical ideas and practices evolve, and ethical authority is tested. Indeed, important structural transformations in the design of medical research and health care have occurred as a result of modifications in public policy and law, following debates over procedural, economic, and ethical considerations of clinical trials.

\textsuperscript{19} For information about professional oversight committees for the ethical and correct scientific conduct of clinical research, see Beauchamp and Childress 326 (2001).
Thus, the legal requirement for a patient’s free and informed consent\textsuperscript{20} to receiving treatment, in the contexts of both health care and clinical research, reflects the importance of the social and ethical problems posed by certain instances of clinical research. In such cases, conflicts of interests and needs between subjects and researchers were not addressed in an ethically rigorous manner, and clinical trials resulted in a systematic abuse of patients. Let us look at two classic examples of clinical research that went awry.

The perilously deceptive Tuskegee syphilis study was a forty-year-long, federally-funded trial that capitalized on the vulnerability of impoverished (and, for the most part, ignorant) African-American patients in Alabama. Although this project was presumed—by its involved patient-subjects—to be a health care venture, it was actually a case of research looking into the natural history of the disease. Before it was forced to termination (1972), and despite the interim development of a syphilis cure (penicillin), patients were not provided the therapy and remained unaware of the real objectives of the study.\textsuperscript{21}

Equally deceptive was a series of non-therapeutic skin experiments in Holmesburg Prison, Philadelphia, which involved inmates, whose incarceration was the source of their vulnerability. Sponsored by the pharmaceutical/cosmetic industry and the U.S. Army in the 1950s-1960s, this research was conducted on healthy individuals, many of whom suffered severe burn, or other physical, injuries. Many of them were seeking the financial resources for their

\textsuperscript{20} An exception to this requirement is allowed in the case of emergency research. This is a hybrid context of research/health care, characterized by lack of effective or safe treatments to respond to life-threatening situations of patients who are unable to communicate, and whose proxy is unavailable to make immediate medical decisions on their behalf. The treatment response to such cases is the application of so-called novel/innovative therapies, which are actually alternative remedies under investigation. For reference to emergency research and consent waiver, see U.S. Food and Drug Administration (FDA), Office of Regulatory Affairs.

\textsuperscript{21} For the story of Tuskegee, see Jones. For an analysis of its moral aspects, see Benedek.
legal representation, and were compelled—and, in a real sense, coerced—to join the trials for the sake of a small monetary compensation. At the same time, the research culminated in numerous prominent publications, patents, repute, and wealth for the dermatologist and principal investigator of the trials.²²

Scandalously, these clinical offenses occurred in an environment of awareness of, and sensitivity to, a clinical research ethics that was growing in the aftermath of an exceedingly atrocious cluster of medical experiments performed in the Nazi concentration camps.²³ Indeed, post-Second-World-War, abuses and murder of thousands of individuals (proscribed by Nazi ideology as genetically inferior and socially undesirable) were revealed to have been part of extensive human experiments conducted by Nazi physicians. This recognition, and the international, legal condemnation of Nazi research, led to the 1946 institutionalization of “The Nuremberg Code.”²⁴ This was the first generally accepted set of guidelines for the ethical conduct of research involving human subjects that articulated the free-and-informed-consent requirement, and instituted the notion of respect for patient-subject autonomy.²⁵

Nonetheless, as the subsequent cases of Tuskegee and Holmesburg indicate, “Nuremberg” had little or no influence on the ways research was conducted in the United States,

²² It is indicative of an unethical research mentality to dehumanize subjects and view them as research material. In the case of these skin trials, and when introduced to numerous inmates, head dermatologist Dr. Albert Kligman was only able to see “acres of skin.” For the story of Holmesburg Prison, see Hornblum.

²³ For references to human experiments by Nazi physicians and investigators, see Proctor 17-31, Pross 32-52, and Mozes-Kor 53-59.

²⁴ “The Nuremberg Code” 431-2

²⁵ Ironically, a number of “exacting” and “progressive” rules for the protection of human subjects in clinical research were “enacted in Germany in 1931 and were theoretically in force until 1945.” Engelhardt 331 (1996)
despite the central role the U.S. had played in the Code’s promulgation. Instead of re-evaluating the effectiveness of the strategies set in motion by the Nuremberg Code, the American medical profession developed new codes to guide research practices in the rapidly expanding U.S. research context.

Thus, the major codes were the “Declaration of Helsinki” (first in 1964 and with several revisions in later years), “The Belmont Report” (1979), and the “CIOMS Guidelines” (1993, revised 2002) focusing on the particularities of international clinical research. Like the Nuremberg Code, these documents emphasized the significance of informed consent as a precondition for providing treatment in a research setting, and this is a crucial element that spilled over into the area of health care as well.

Social communities and the social institution of clinical research

The enterprise of clinical research has been broadened in recent years to include diverse communities engaged in ongoing dialogue (and often dispute) as they negotiate rights, claims, and special interests. Thus, apart from the medical research industry deliberating on the design of new therapies and trials, and the political and business leaders dealing with the economic and

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26 In English the spelling has changed into “Nuremberg.”

27 World Medical Association 433-6

28 The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 437-48

29 “CIOMS” is an acronym for the Council for International Organizations of Medical Sciences, which developed this code of guidelines in collaboration with the World Health Organization (WHO) in 1993. This code was revised in 2002. The Council for International Organizations of Medical Sciences [CIOMS] (2002); 501-10 (1993)

30 Curiously, the phrasing of this condition differs in each instrument, a fact that entails substantial variability in the consent process that each document seems to require. Levine, R.J. 236 (1996)
socio-political implications of proposed studies, a number of social groups are also involved. Among them are groups representing populations of research subjects and negotiating the terms of these patients’ participation in trials. Others are activists advocating subjects’ ethical treatment in research. This may include a number of things, such as entitlements to health care following the end of trials and the development of treatments, or even subjects’ claims to intellectual rights in the production of (lucrative) drug therapies.

Advocates of vulnerable participants (i.e. children, women of childbearing age, the mentally impaired, or the incarcerated), as well as religious organizations, are also part of similar public discussions as they uphold their own viewpoints of ethical clinical research, and exert influence for the legal authorization or prohibition of specific medical/research practices. Still, other groups require the development of new life-saving therapies to benefit present and future patients, and even press for substantial legislative and structural modifications in clinical research in order to accelerate the drug development process.\(^{31}\)

It can thus be argued that clinical research has emerged as a social institution in its own right, insofar as we think of social institutions as systems of modes of behavior leading to social relationships, and persisting through time.\(^{32}\) We have seen how clinical research, as an institutionalized activity (or a set of modes of behavior), is characterized by specific norms and values, to which the involved individuals and groups must conform, or face pain of sanction. Looking at its history, we see that research involves \textit{socially reproduced} practices (as is the

\(^{31}\) The case of the 1980s AIDS activism, principally spearheaded by the gay community, has already been mentioned, and presents an example of social influence in transforming the processes of clinical research. Levine, C. 108 (1996); Specter 56-65

\(^{32}\) The notion of social institution that is used here is based on Anthony Giddens’s account of “institutionalized activity” and ”mode of conduct,” as opposed to the ideas of group or collectivity, to which the term ordinarily refers. Giddens 9-12
experimentation on humans), and recurring modes of belief (as is the moral sensitivity to and norm of protecting human subjects). We are now about to see how clinical research involves social relationships reproducible not only across generations, but also across societal and cultural borders.  

Transnational clinical research

The aforementioned multitude of communities involved in the processes of clinical research has been enlarged significantly in the last two to three decades by the addition of another group: a large population of Third world citizens who participate as subjects in clinical trials sponsored by Western clinical research agencies. Typically hosted in developing countries, transnational research usually involves patient-subjects who are in (urgent) need of medical attention, and willing to try new—albeit still experimental—therapies.

Yet, such trials are predominantly conducted to study pathologies of interest to Western patients (e.g. AIDS), whereas infectious and vector-borne diseases (e.g. lymphatic filariasis, onchocerciasis, and dengue fever endemic to Africa, and even the plague, banished from Europe a century ago) remain largely under-investigated and mostly un-remedied. Cynical though it may sound, the (Western) drug industry strives to develop profitable therapies that are purchasable—for the most part—in the West, while dismissing therapies that are referred to as orphan drugs. According to the U.S. Orphan Drug Act (passed in 1983), these drugs would respond to diseases defined as rare (or “orphan”) because they affect fewer than two hundred

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33 It is evident that there are variations to these relationships across space and time, but their basic elements are preserved so that we may speak of the same institution.

34 Farmer 305
thousand individuals in the United States, hence orphan products lack cost-effective benefit for the drug industry.\(^{35}\)

In such transnational and cross-cultural contexts, clinical research becomes a vehicle for a multifaceted exchange that connects the local governments and medical establishment with international health organizations and Western researchers (i.e. the World Health Organization, European and American pharmaceutical companies, academic biomedical investigators, etc.). This web of joint efforts embodies the medical face of a broader economic and political interdependence (and exchange) between the technologically developed nations (sponsors of clinical research), and the developing ones (hosts).

The international research endeavor is part of the broader social institution of clinical research as already analyzed (indeed, it may be thought of as a global institution). Its actors, and mainly the physician-researchers and patient-subjects involved in it, are motivated by the same aspirations, and perform their tasks with the same intensity, as their counterparts in the West. As will be seen later, the economic and technological dependence of developing and resource-poor nations on the wealthy and industrialized ones is a major factor shaping the international research process. This is not surprising because relations of power (whatever their source) are part and parcel of any social institution, and especially one of global reach and scope such as transnational clinical research.

The moral debate in transnational clinical research

The global expansion of the research enterprise, owing primarily to the pressing need for new therapies both in the West and the Third world, has brought about an intense (and, as yet,  

\(^{35}\) The Act has been amended and current law provides some incentives for the development of orphan drugs. Dept. of Health and Human Services
unresolved) debate whose main issue is whether “the same principles of research articulated in the West ought to be required of clinical research jointly conducted by developed and developing nations.” This discussion, which raises doubts about the universal validity of a single set of ethical principles applying to clinical research conducted anywhere, has far-reaching implications in both a philosophical and an anthropological sense.

For one thing, any doubt about the justification of a universal (and universalist) research ethic challenges the philosophical/ethical underpinnings of the Western analytical moral thought, in which universality is one of the underlying themes. One such universalist approach to human morality is expressed in the corpus of political liberal philosophy, which includes such classical proponents as Hume, Mill, Paine, and Thoreau, and most recently John Rawls writing on justice. Political liberalism is organized around the basic concept of individual liberty, and its institutional safeguards (i.e. constitutionally-limited government, the rule of law, etc.) that comprise a list of (human) rights, originally articulated as “natural,” and as applying to all people by virtue of their being human (hence their universality).

Based on the notion that the point of morality is to promote the wellbeing of others, and by rooting this conception of wellbeing in the physical, emotional, and intellectual constitution of people, human rights have developed into a sustained authoritative discourse that has led to improved behavior by states and other structures of authority the world over. Despite its inadequate implementation that leads to frequent (albeit internationally condemned) violations, the human rights discourse has informed the various codes of bioethical principles that guide

36 Vanderpool 223

37 It can be said that the most authoritative political articulation of rights conceived in the liberal light to date is the Universal Declaration of Human Rights adopted by the U.N. General Assembly in 1948.
transnational clinical research in the universalist direction, offering (according to universalists) the only kind of normative framework that can insure the protection of subjects from trial abuses and exploitation.\textsuperscript{38}

At the same time, epistemological doubt has been expressed about the universal validity of a single research ethic, thereby ushering the concept of difference (of some kind) that may legitimately create differentials in the research procedures implemented in diverse societies. This difference is defined by an infinite cultural diversity, generated by local societal and cultural forces, that gives rise to unlimited ethical plurality across nations (many of which partake in the research effort). Cultural plurality is then purported to legitimize several, and not one, moral frameworks that can guide the processes of clinical research (in spite of its being a commonly, and globally, shared social institution).

The pluralist approach to ethics recognizes that ethical norms and principles (including those guiding clinical research) are produced and negotiated through discussions occurring within specific historical and cultural contexts, and are shaped by local belief systems, power relationships, and individual everyday-life experiences.\textsuperscript{39} Their variation from culture to culture, ethical pluralists will argue, makes it inappropriate to apply a single set of ethical principles to medical practices in all societies and communities participating in the research process.

According to the pluralists, a universalist approach would imply Western ethical superiority, and would constitute a Western cultural/ethical imposition upon non-Western societies. Indeed, it would amount to yet another form of exploitation in the form of “ethical imperialism,” as the universalist view has been branded by the more radical adherents to the

\textsuperscript{38} For a defense of universalism, see Macklin.

\textsuperscript{39} For a defense of the pluralist position in clinical research, see Levine, R.J. 235-56 (1996).
difference-based approach.\textsuperscript{40} Therefore, a combination of ontological/cultural and
deontological/ethical claims are employed in advancing the argument of ethical pluralism.

The pluralist position has been an adaptation of the descriptive and normative theses of
relativism to the conceptual and normative frameworks of clinical research ethics. Introduced in
the second half of the nineteenth century by the emerging field of cultural anthropology, the idea
of the relativity—as opposed to the universality—of values across cultures was received
favorably by many continental philosophers, and became a leading unifying notion of the
otherwise disparate strains of postmodern thought. It also remains the underlying philosophical
premise of contemporary cultural inquiry, which exhibits a plethora of conceptual and
methodological directions.

The history of relativism within American anthropology had been a complicated one
throughout the twentieth century. The immense cultural and moral diversity across societies and
cultures that was revealed through extended ethnographic work established the cultural relativist
thesis. However, several anthropologists (i.e. Linton, Redfield, and Kroeber) were arguing in the
1950s that certain standards of value and moral judgment are commonly shared by all societies,
and thereby transcend cultural boundaries.\textsuperscript{41}

Yet, ethical relativism, as a sound moral theory calling for the tolerance of, and respect
for, norms and practices the world over, could not be derived from the cultural position. An
anthropological narrative describing beliefs, values, sentiments, and customs, as well as their
historical sources, can enrich our cultural and ethical understanding, but it does not justify claims

\textsuperscript{40} Likewise, universalists accuse pluralists of “ethical relativism.” To have an idea about this
controversy with respect to transnational clinical research, see Angell (1988).

\textsuperscript{41} Hatch 106-9
of, say, coercion and violence. That is, an “ought” may not be derived from an “is.” The case of Nazi norms and practices during World War II makes it clear that relativist ethics can be neither sanctioned nor endorsed.\footnote{The post-war U.N. Declaration of Human Rights is an affirmation of this point.}

The philosophical currency of relativism, fluctuating between high and low points throughout its life, is still being debated today.\footnote{Hatch 104-32} It is against the backdrop of the (ethical) universalism-vs.-relativism dichotomy that the technical configuration and ethical issues of transnational clinical research, are contested and negotiated.\footnote{For an extensive discussion of relativist ethics and universal values in medicine, see Macklin.}

The ethical pluralist model

It is beyond the scope of this thesis to rehearse the strengths and weaknesses of universalism and relativism, but the proposal for a hybrid model that seeks to circumvent the aforesaid dichotomy and its related problems in the context of international clinical research deserves mention. This is the thesis of ethical pluralism, which recognizes culture as the cradle of all ethical systems, and thereby allows for a socio-cultural origin of moral values and ethically acceptable practices, including those related to medicine and clinical research.\footnote{For an explication of the ethical pluralist model, see Christakis 261-80.}

Most importantly, ethical pluralism refuses to polarize the controversy about ethically acceptable norms and practices between the extremes of the universalist and relativist positions. In fact, it claims to be superior to both on account of the normative flexibility it allows in the negotiation of ethical disputes that inevitably arise in transnational (and, hence, transcultural) clinical research. This flexibility is expressed in two ways: First, the model refuses to rigidly
apply the established ethical guidelines for international research by excluding all non-Western understandings of medical ethics. Such conceptions may not exist in a formal sense (as would be the theoretical structure of Western medical ethics), but may be rather incorporated in the socio-moral fabric of the society and culture hosting research.

Second, ethical pluralism brings various types of frameworks to a dialogue and mutual evaluation, negotiates their discrepancies, and seeks to resolve arising problematic situations. Such frameworks include bioethical (say, research) guidelines, but also social, political, and ultimately cultural systems. Ethical pluralism considers cultural analysis to be “integrally related to moral analysis,” and tends to classify clinical research ethics along with “other socio-political and religious thought.”46 It, therefore, claims to celebrate a contextualist view of medical ethics.

Moreover, ethical pluralism is reconciled with the prospect of abandoning a research project once it becomes clear that the desired negotiation-among-equals setting that the model requires is unattainable when differences between distinct cultural/ethical frameworks are insuperable in specific circumstances. Whatever its degree of success, ethical pluralism seems to be pursuing the development of a procedural ground in the context of international research, where it may be possible to bring the more flexible strains of universalism and relativism into a joint kind of action.

Ethical incommensurability in clinical research across cultures

As previously stated, the debate about ethical frameworks applicable to international clinical research is yet unresolved, but this may not be a setback to the intellectual endeavor of theorizing and assessing the justification of clinical research practices. On the contrary, as discussions have been expanded to include socio-economic, political, and cultural considerations

46 Ibid. 270
about communities and other forces involved in international research, the ethical basis for research evaluation is broadened beyond the theoretical and normative context of conventional bioethics. As a result, a contextualist approach to the medical ethics of international clinical research seems possible, and that may create a bioethical framework that is conceptually enriched and open to alternative methodologies.

Such methodologies need not depart from the dominant theoretical framework of Western biomedical ethics. This is a bioethical model based on four specific principles that provide the normative grounds for the various extant sets of guidelines used in international clinical trials. The principles (which will be explicated in detail in the third chapter of the thesis) are those of respect for autonomy, nonmaleficence, beneficence, and justice.47

Yet, ethical guidelines for international research (based on the aforesaid principles) may be found incommensurable with the cultural and moral norms of local individuals and communities participating in clinical studies. Such local norms might be conceptions of personhood grounded in a value system that is based on notions of community, rather than the Western values of individualism and autonomy. However, a collective ethic may render the requirement of, say, free and informed consent (a standard item in research guidelines) incomprehensible for local persons, and hence does not warrant insistence on such a requirement.

In this case, the model of ethical pluralism suggests that differences in cultural and normative values may require value negotiation and flexible adjustment of international research guidelines to local standards (unless ethical incommensurability is too great to warrant this move). Other authors claim that the discrepancy in values simply signals the need for a re-

47 Beauchamp and Childress 57-282 (2001)
evaluation, and even revision, of the guidelines at hand. This suggestion may raise the suspicion of a prospect for unethical research motivated by an “anything goes” attitude.

Yet, this proposal also claims to be based on the contextualist assertion that dialogue across cultures is possible. In avoiding literal translations in cross-cultural communication that frequently cause confusion, the argument goes, our effort should instead focus on the significance of revealing the local “underlying symbolic and idiomatic meanings” that may expose “shared meanings” between Western researchers and Third world subjects and communities. This proposition assumes that, at the end of the anthropological inquiries it advises, local cultural values are bound to prove compatible with the basic bioethical principles guiding international research.

For instance, the previous example of community-based understandings of personhood suggests that the consent requirement be replaced by one that involves permission given by community elders to prospective subjects to enter clinical trials (if this is the local custom). This would still be in line with an interpretation of individual autonomy that respects people’s choice (molded by culture, to be sure) to delegate the power of decision to respected persons of authority.

However, this anthropologically-based proposal does not examine the possibility of finding no “shared meanings” in the end, hence an eventual incompatibility of local norms and bioethical principles. A skeptic might thus argue that the recommended modification of guidelines, in line with the specific socio-cultural environment of research, is unwarranted, and seems to only suit the needs of researchers.


49 Ibid.
What is more, in the real world of power relations, “traditional” societies tend to selectively curtail the decision-making power (that we associate with rights and freedoms) of certain individuals (e.g. women) on the grounds of some purported protectionist normativity, and confer it on other persons of authority (e.g. “village elders,” male family members, etc.) in the form of morally sanctioned “responsibilities.” In the guise of tradition, the resulting social and political powerlessness of certain groups easily leads to the trampling of their basic, vital possibilities, including that of deciding what to do with one’s body.

**HIV/AIDS clinical trials in the Third world and the issue of research justice**

Probing the various aspects of international clinical research includes its ethical scrutiny, particularly with regard to complex and challenging issues of justice (that will be explored in the third chapter). As noted earlier, this thesis will examine a series of HIV/AIDS international trials that were mostly conducted in sub-Saharan Africa. The decision to explore these particular studies is justified by the fact that ethical issues of research (generally speaking) have a special edge when it comes to international research because of Third world demographics associated with the disease.

Indeed, nowhere in the world has AIDS taken a greater toll in human lives than in developing nations. Sub-Saharan Africa, certainly the hardest-hit area worldwide, “is home to close to two-thirds of all people living with HIV—some 25 million,” whereas its population is only just over 10% of the world’s population.\(^{50}\) On the other hand, only an estimated 1.6 million people living with HIV are to be found in high-income countries.\(^ {51}\)

\(^{50}\) UNAIDS

\(^{51}\) Ibid. 37
As the epidemic has claimed the lives of the younger and most productive segments of the population in the most devastated areas, it has produced enormous social and economic problems in leaving behind millions of orphans and elderly dependents uncared-for, students without teachers, and services without civil servants. Sub-Saharan Africa has thus seen decades of economic and social progress being erased, and life expectancy reduced by decades, while the slowing of economic growth and the deepening of poverty have exacerbated chronic shortages of food and clean water.\textsuperscript{52}

In addition, the management of the infection/disease in the Third world is tightly connected with economic conditions that shape the structural capacity of these countries to address HIV/AIDS and its social consequences. The perennial international debt of the Third world, lack of meaningful aid for development, the pervasive corruption of most of its political leaders, and the prohibitive prices (set by Western pharmaceuticals) of the major retroviral drugs make it nearly impossible for Third world governments to respond successfully to the epidemic.

Moreover, the economic structural adjustment that globalized economy has demanded of the Third world, and which aims at increasing privatization, undermines publicly funded programs of, say, health care. At the same time, rampant unemployment in urban centers has resulted in the migration of large male populations, seeking work, to rural mining areas, and in their separation from their families for extended periods of time. Such displacements breed risky sexual behavior that undermines the health status of men, women, and children, and cultivates the social conditions that spread the infection.

The severe impact of AIDS on Third world populations has been used by the agents and structures of the international research effort (including those of the Third world) as a reason to

\textsuperscript{52} Ibid. 41
justify the implementation of extensive clinical trials in these countries. The claimed goal of this research is to identify local particularities in the biology of the disease in order to help generate appropriate therapies that would benefit these (and probably other) populations. But it is also likely that governments in Third world countries, with little appropriate medical infrastructure, typically welcome Western-sponsored research as a response to their limited resources for health care.

Clinical research is, therefore, more-or-less integrated within the everyday life of Third world citizens as (often) being the only form of available medical care. Therefore, justice in research becomes part of the general social justice in the lives of local individuals and communities. In this context, an ethical analysis of justice in transnational clinical research can be reasonably part of a larger discussion of Third world development and, specifically, of the establishment of certain political goods such as the ones emphasized by the human capabilities approach we will present (albeit briefly) in the third chapter.

Bioethical discussions of justice, or other issues, in clinical research are typically limited to terms that are used for analyzing, negotiating, and resolving problems on the basis of ethical arguments and theoretical models. The usual aim is to anticipate problematic situations that can arise from the implementation of research protocols, and to provide ethically acceptable structural solutions so as to manage such problems in a procedural way. The fact that

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53 The term “Third world” conceals significant social, cultural, political, and economic differences among the many countries it denotes. Although the majority of them have had, or are projected to have, a serious AIDS problem, countries such as Brazil have taken effective steps in managing HIV/AIDS on their own by setting up their own generic drug industry, and against the grain of international trade patterns that protect the interests of Western drug companies.

54 These resources are often limited in part by governments’ choices to invest on other goods, such as weapons.
transnational clinical trials take place within the big picture of want and disease in the Third world is not very relevant in these bioethical analyses.\textsuperscript{55}

This chapter has mapped the landscape of clinical research as a social institution of global scope. As such, clinical research has been shown to mobilize a diversity of other institutions such as health and health care, science (through the production of biomedical knowledge), the pharmaceutical industry, activism for health care and human rights, legislation and policy, and academic inquiry in philosophy/ethics, society, culture, and economy.

In this landscape, I have situated questions about the adequacy of specific theoretical frameworks in assessing justice, and most importantly, justice in research conducted in the Third world, and I have underscored the importance of looking into HIV/AIDS transnational research. I now turn the discussion to a more microscopic analysis of clinical research that includes an account of its conceptual structure, as well as of the notions upon which the ethical framework of present-day bioethics has been constructed.

\textsuperscript{55} One of the aims of this thesis is to suggest that a broader ethics may be needed to address bioethical issues of research by taking into account social inequality, oppression, and human deprivation of basic goods that may enable people, not simply to survive, but to create and sustain flourishing lives. As mentioned in previous pages, this terribly important topic cannot be fully developed in this thesis, but relevant issues will be brought to the fore in the last chapter as a suggestion for further future analysis.
CHAPTER 2
THE CONCEPTUAL BASIS OF CLINICAL RESEARCH

Multiple understandings of clinical research

Having charted the social topography of clinical research in broad brush strokes, so to speak, we have gained insight into what it encompasses: an ever-growing body of scientific and medical knowledge, a wealth of technologies and human resources, and a diversity of intellectual activity that includes the management of illness in patient-subjects, even when pursued at an experimental (and thus limited) level. Because these features of research aim at outcomes linked with human life, they have an inherent moral substratum that relocates them from a strictly scientific realm into the social sphere, whereby they can be ethically analyzed and assessed.

The moral acceptability of biomedical research is connected with the ways individuals perceive it as affecting life and health at the individual and social level. As was seen in the previous chapter, research operations are highly complex because they are located in, and transcend the borders between, multiple contexts: scientific, medical/clinical, political, economic, social, and cultural. In addition, transnational clinical research enters into social and cultural spaces shaped by different histories and engendering diverse responses to life.

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56 For instance, embryonic stem cell research, anticipated to make enormous therapeutic breakthroughs in debilitating conditions (e.g. Alzheimer’s disease), is welcomed by scientific investigators and, to a considerable extent, by the general public as socially beneficial. Yet, because it involves the sacrifice of embryos, which is perceived as tantamount to murder by some religious individuals and anti-abortion advocates, stem cell research is also considered, by many others, as morally unacceptable and socially pernicious.

57 This is also true (on a smaller scale) for any single country with a plurality of social and cultural groups, as is the U.S.
Within the multiplicity of these environments, the conduct of research is responsive to the kinds of knowledge and conceptualizations various actors may have of human experimentation, and this sphere of conceptual understanding is also shaped by people’s particular value systems. Research projects are thus ethically evaluated on the basis of wide-ranging concepts, more or less (or entirely) different, depending on the philosophical and ideological frameworks in which research is viewed and understood.

For example, approaches to clinical research as an instance of health care, or as a purely scientific/biomedical endeavor, or even as a tool for lucrative gain, have already been mentioned. Similarly, certain religious and/or metaphysical conceptions of life may look upon medical research as a human (and, usually, ethically unwarranted) intervention into states of affairs that are thought to be divinely- or metaphysically-determined.

Moreover, these conceptions form the breeding grounds for various political agendas with regard to the costs and benefits of research, and their distribution among the parties involved. As a result, an intricate web develops of perceptions, considerations, necessities, interests, goals, and strategies by all who participate in research projects, and invariably gives rise to ethical questions related to research processes and objectives. Therefore, the task of those engaged in reviewing research proposals—including research investigators, the very persons who are ultimately required to conduct morally justified studies—consists in clarifying, and reasoning out, interwoven complex issues so as to generate responses that can translate into ethically acceptable research procedures and outcomes.58

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58 The content of (ethical) acceptability is a question that will be revisited later.
The moral scrutiny of clinical research is part of a broader ethical analysis\(^\text{59}\) that, for practical purposes, is usually structured to involve three steps:\(^\text{60}\) First, one defines problems of medical interest that raise ethical issues (a metaethical sort of work); second, a theoretical framework is generated for the systematic ethical study of these issues (a methodological step); and third, normative procedures are established, usually in the form of applicable guidelines, to help those who work across the spectrum of health policy\(^\text{61}\) to make the right decisions (a prescriptive effort toward regulation). Indeed, these guidelines form the prescriptive end result of this intellectual process—the distillate, so to speak, of its ethical implications.

This series of steps reflects an analytical, if reductive, approach to moral concerns about clinical research. It also represents a *regulatory* model of research assessment, for this approach eventually aims at *peer review* of proposed research protocols by IRBs (Institutional Review Boards), and *inspection*, by oversight committees, of the research procedures that will unfold subsequently. IRB review in particular is instrumental in establishing requirements of formal procedures (e.g. the process of voluntary and informed consent) at the structural level of the research project as a means of safeguarding the physical and psychological wellbeing of subjects, and upholding certain moral standards.

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\(^{59}\) This analysis extends to all issues across the spectrum of medicine, including questions of *health care resource allocation* and *occupational-environmental protection*. These areas of concern, along with *biomedical research*, comprise the three broad domains in the general sphere of *health policy*. Powers 147

\(^{60}\) Callahan 87-9

\(^{61}\) The same ethical codes of clinical research apply to jurisprudence, whereby moral considerations of the same sort inform the legal scrutiny of contested health policy decisions. For a brief consideration of some court cases involving ethical problems in medicine and health policy, see Beauchamp and Childress 415-31 (2001).
Therefore, the ethical deliberation, assessment, justification, and regulatory practice for any single research project constitute a linear progression of phases organized around a single set of guidelines. These rules are based on ethical claims that are, in turn, grounded in pre-existing conceptual foundations that consist of metaphysical, epistemological, and moral propositions. The main point here is that these assertions are accepted as valid, and as central to the nature of biomedical research involving human subjects.

For instance, understandings of personhood, views on the predicament of illness and the social meaning of research, or even epistemological positions that are used to ground human experimentation as a scientific endeavor, are some of the types of conceptions at the root of (the idea and practice of) clinical research. Underpinning this groundwork are certain key notions, such as those of the human body and person, health, illness/disease, the individual and social good, knowledge and empirical science. It is by building upon these primary concepts to form a discourse of specific ontological, epistemological, and ethical understandings that the conceptual and methodological structure of human clinical research, and a co-existing regulatory mechanism for it, can be constructed.

Mutable primary concepts in the ethics of clinical research

As mentioned earlier, ethical reflection on clinical research is shaped by particular philosophical and ideological systems in the context of which research is to be comprehended. As a biomedical project involving patient-subjects, research partakes of both clinical practice (medicine as care) and human experimentation (medicine as science), despite a general tendency to equate it solely with science. As a result, various ethical issues arising in both of these sub-domains help to construct the ethical discourse of clinical research, in which the aforementioned notions of the human body and person, health and illness, society and the good, knowledge and
Science, along with the nature of medicine and the physician-patient relationship, are fundamental.

Therefore, an analysis of at least some of these concepts is, at this point, necessary to provide a deeper understanding of clinical research and its ethics. Far from being firmly established, these concepts not only acquire variable meanings through time, but, even at any given moment, they inhabit—as we shall see—various socially- and culturally-shaped significations. I will focus primarily on the notions of health and illness, while meanings of the other concepts will be emerging from this analysis. My immediate objective is to show that there is little constancy, no fixity, and relative mutability in these conceptions.

Thus, health is typically described as the desirable state of bodily and mental wellbeing, which is regarded as normal, and is usually defined negatively in terms of absence of disease. However, in a biological context, wellbeing (whether anatomical, physiological, and/or psychological) has meaning only in response to a certain conception of the body and mind’s ability to perform vital functions. In this sense, health may be thought of as an organism’s capacity to maintain itself, given the biological possibilities open to its species—a fact that has a bearing on the preservation of the species as well.

62 The World Health Organization has offered a positive definition of health, whereby “health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.” World Health Organization

63 According to a standard medical definition, health is: (1) “the condition of an organism or one of its parts in which it performs its vital functions normally or properly: the state of being sound in body or mind; especially: freedom from physical disease and pain,” and (2) “the condition of an organism with respect to the performance of its vital functions especially as evaluated subjectively or nonprofessionally.” Merriam-Webster Dictionary, Medline Plus (health)

64 Engelhardt 32 (1981)
Yet, if health is a measure of anatomical integrity and physiological potency, it is unclear whether the aging-related degeneration of vital functions should count as disease. In addition, the concept of wellbeing is connected with the ability of an organism to adapt successfully to its social environment from a physical and/or mental standpoint. However, the degree of this adaptation, and the specificities of any social context to which one must adapt, render the notion of wellbeing very fluid and ambiguous. Even if we were to posit a state of “complete” wellbeing as a condition that defines health, we should then question whether anyone could ever be truly healthy, or whether everyone is more-or-less ill.

This reflection points to an overlap between the notions of health and illness/disease, and as a result, the effort to comprehend the former without having an idea of the latter cannot be fruitful. Moreover, it should be noted that, although disease is the leading medical term, we refer to illness when we think of impairment from the viewpoint of the suffering patient. The distinction between the two terms implies that a person can have a disease without (yet) showing symptoms of illness, and one can feel ill (or “under the weather”) without having a disease per se. Therefore, illness is defined as a cluster of symptoms, whereas disease accounts for an etiology; that is, an identified cause.

Therefore, the concept of disease refers to “the impairment of the normal state of the living animal or plant body, or one of its parts, that interrupts or modifies the performance of the vital functions, and is a response to environmental factors (as malnutrition, industrial hazards, or

65 Ibid.

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67 Engelhardt 32 (1981)

68 Ibid. 33
climate), to specific infective agents (as worms, bacteria, or viruses), to inherent defects of the organism (as genetic anomalies), or to combinations of these factors.” As such, disease is perceived as an abnormal, disturbing, and undesirable condition of the body and/or the mind.

Moreover, in defining disease as impairment (physical, psychological and, by extension, behavioral), one designates certain conditions as unpleasant, and thus undesirable, as opposed to others that may be perceived as attractive and preferable. In this sense, the concept of disease is a normative one, suggesting states of affairs that “ought not to be.” In addition, what is termed diseased can be labeled as ugly, pointing to an aesthetic conception of disease, or perceived as the negation of the good, thus implying the ethical directive that one should actively seek to bring about the “good” and eliminate the “evil.” In this respect, the concept of disease legitimates certain social expectations as ethical, thereby raising particular obligations and removing others.

The conceptual foundations of clinical research as belief system

Yet, the elucidation of the concepts of health, disease, and wellbeing seems to require an examination of the idea of normalcy—and its opposite, abnormality. The meaning of (ab)normal (as regards the function of the body, or anything else for that matter) refers to the degree to which anything deviates from a certain standard, or norm (we commonly understand

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69 Merriam-Webster Dictionary, Medline Plus (disease)

70 Here the distinction between body and mind is not meant to emphasize a body/mind dichotomy, but simply to include both of these categories as being basic in what we typically associate with the human person. From now on, “body” will be used to denote the mind as well.

71 Engelhardt 33 (1981)

72 For instance, persons in the social role of the physician are duty-bound to care for the sick, while there is a moral basis to having one’s social obligations relieved (at least temporarily) when one is ill.
normalcy in terms of degree). Setting appropriate criteria for evaluating how anything compares with the accepted standard represents an evaluative act, which is part of a broader process that includes the steps of determining who will conduct this assessment, and how the norm will be defined in the first place.

None of these steps is explanatory (as, for instance, would be the case of describing a natural state of affairs or procedure that is unaffected by human will); rather, they are evaluatory, with outcomes determined by parameters that—as I will try to show—cannot be definite, stable, and permanent. Why is this so? For one thing, establishing a norm is a problematic issue, because claims of truth that are instrumental in introducing and sustaining norms are open to discussion, rather than grounded in indisputable facts. The same is true of the other two steps, because the entire process is a belief-gaining practice.73

It is necessary, at this point, to linger for some time on an epistemological analysis of what it means to generate beliefs, which are the substantive building blocks of both common and scientific reasoning (scientific hypotheses/theories are coherent belief systems; e.g. medical definitions or models of health and disease). The point here is to show philosophically that the conceptual foundations of clinical research (excepting the primary notions of health, disease, and the like) consist of beliefs that are not independent of social values and cultural influences.

Such beliefs are related to the structural features of research as a scientific project, and are statements of scientific theories, which, if shown to be socially-shaped, should then be seen as destabilized elements of a (scientific) discourse that is penetrated and influenced by social and cultural values. This can be the case even if we retain certain, in some way, epistemological...

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73 Coming up with any assertion that we judge to be true (whatever our criteria) is an instance of either “generation, selection, evaluation [or] consolidation of [an] acceptable belief.” Science is the supreme example of institutionalized belief-gaining practices. Lacey 51
structures such as scientific *impartiality* and/or *objectivity* (as we shall see in the theories of science that will follow).

**Beliefs, cognitive values, and belief-gaining practices**

Beliefs are propositions, or “propositional attitudes, that, together with desires, intentions, having goals and the like, may play causal roles in generating actions.” As statements, beliefs may be true or false, depending on whether their propositional content is found—after proper evaluation—to fulfill the ideal of *truth*. Far from being a metaphysical category of some absolute value, truth is understood (in this context, at least) to be the *knowledge* imparted by the claim a belief makes.  

Whether this knowledge (i.e. a belief’s *content of truth*) is worth accepting as valid is a matter of considering and appraising appropriate criteria that have been used in forming the belief. For instance, in the case of beliefs that we may characterize as “scientific,” as well as for many *commonly-held* beliefs, various criteria should obtain: grounding the belief in evidence, establishing this evidence upon the use of acceptable empirical data, entailing the belief from other true beliefs through proper inductive or deductive inference, satisfying rational canons, and so on.

These items are clearly about attributes, and relations with other beliefs, that the belief under examination may be thought to possess, and in virtue of which it is appraised. If the agent who makes the assessment thinks that the content of the belief under scrutiny follows rationally

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74 Ibid. 46

75 Truth is not the only principle that is aimed for in the context of gaining a belief. If a belief is to inform action toward a proposed goal, it must also be evaluated in terms of the value of *relevance*, or *significance*, with regard to the specific goal. Ibid. 48

76 Ibid. 45
from criteria that are acceptable (in a specific context of analysis), the belief is affirmed as true, and is thus gained (according to Lacey’s terminology) as opposed to being rejected. These criteria are the cognitive values of the belief, and are part of the value complex\textsuperscript{77} of the agent who makes the assessment.\textsuperscript{78}

From this sketchy account of how beliefs (and theories, including scientific ones\textsuperscript{79}) come about, one can imagine that what might count as cognitive values can have tremendous implications on the (resulting) beliefs people come to hold, and the actions they take as a result of these beliefs. Setting aside scholarly debates about the characteristics of cognitive values (and related issues), one question is of salience for our pursuits: to check the possibility that cognitive values (and, by extension, beliefs) might be socially-constructed. In other words, we should examine whether social values enter, and somehow shape, the processes and outcomes of scientific inquiry.

If it were possible to show that cognitive values of science (and, by extension, of scientific beliefs) are (to some degree) socially constructed, then science—and scientific beliefs/theories—could not be declared as social-value-free. In such case, one could argue that the conceptual framework of clinical research has a socio-cultural source. Moreover, the fact that moral thought and theory are based on gained (ontological) beliefs about phenomena, and

\textsuperscript{77}Defined as the “ensemble, set, cluster, scheme, outlook or perspective” that are “woven into a person’s life,” or embodied in institutions, a complex of values includes personal, social, moral, aesthetic, and other values that, in certain formulations (i.e. Lacey’s), are distinct from cognitive ones. Ibid. 30

\textsuperscript{78}Ibid. 45-6

\textsuperscript{79}Generically, scientific theories are scientific beliefs that have been validated, or “gained,” through an appropriate evaluative process. Before validation, such beliefs are typically known as scientific hypotheses.
employ these beliefs to make ethical judgments, means that any ethical reasoning of research-related issues has a social and cultural component at its conceptual basis.

Because a social and cultural origin of commonly-held beliefs can be easily postulated, it is better to conduct this examination in the context of defining what constitutes the scientific inquiry, whose cognitive processes are held—at least by the long-standing positivist tradition—to be (and to render science) free of social value and influence, and thus impartial. An ongoing epistemological contention about the value-free-science paradigm also helps to emphasize the role of values (whether cognitive or non-cognitive) in the generation of scientific beliefs, rather than in other types of belief-gaining practices. For these reasons, I will go on to present two brief accounts of the so-called scientific method as a way of exploring the social character of scientific beliefs.

In selecting appropriate theories for this analysis, I need to exclude polarized approaches to knowledge and scientific inquiry, for they lead to diametrically opposite conclusions, whose validity cannot be explored within the scope of this thesis. Such perspectives are, typically, either strictly positivist theories of knowledge, or radical postmodern theories of science. More to the point, as the former theories are committed to a full ideal of value-free science, they allow no room for the possibility of social influence in the domain of scientific investigation. Conversely, by advocating a purely relativist conception of knowledge that is socially and culturally determined, the latter set of theories reject objectivity as the handmaiden of a power-driven and biased science, whose claim to true knowledge they regard unjustified.

However, differing—and, in a certain sense, contrasting—epistemological views of scientific inquiry that allow for common ground, whereby the role of social values in science may be examined, can be insightful and useful. Such views are offered by Hugh Lacey’s
empiricist account of the role of cognitive (and non-cognitive) values in science,\textsuperscript{80} and Helen Longino’s contextualist empiricist theory of scientific inquiry that endorses a feminist conception of objectivity.\textsuperscript{81} Both theories converge in their mutual acknowledgement of the role of social values in shaping scientific beliefs, although they offer divergent explanations of how this is done.

**Lacey’s account of socially-neutral cognitive values in science**

In his monograph *Is Science Value-Free?*\textsuperscript{82} Lacey offers an analysis of how scientific inquiry is connected with values, which he categorizes into cognitive on the one hand, and non-cognitive, or social, on the other. Although he gives a negative answer to the question in his title (for reasons to be clarified shortly), and goes on to explain how social values (i.e. socio-cultural constructs) pervade the effort of gaining scientific knowledge,\textsuperscript{83} the author is in fact committed to an ideal of a (social) value-free science, at least insofar as the scientific endeavor is the result of value-free cognitive processes. These, in the author’s view, are exclusively driven by cognitive, as opposed to social, values.

This distinction is an essential presumption for upholding the notion of impartiality in science, which—in line with the traditional empiricist epistemology of scientific knowledge—Lacey regards as the core value for the acceptance of sound scientific theories. Scientific impartiality means that the cognitive processes, intrinsic to the evaluation and acceptance (or rejection) of a scientific belief, are such that a candidate theory’s “confirmation, corroboration,

\textsuperscript{80} Lacey

\textsuperscript{81} Longino

\textsuperscript{82} Lacey

\textsuperscript{83} Lacey’s stance with regard to the role of social values in science is partly normative and partly descriptive. Indeed, he claims that social values “must” pervade science. Ibid. 256
verisimilitude, or truth" is adequately demonstrated in light of empirical evidence. This evidence consists of considerations of empirical data, as well as already accepted relevant theories.

Every criterion, or cognitive value, entering the evaluative processes of science (which can be thought of as scientific-belief-gaining practices) is, in Lacey’s view, independent of any personal, social, or cultural influence. This means that no hypothesis, competing for acceptance against other candidates, is favored on account of some social, or personal, or other non-cognitive value. Therefore, all (gained) scientific theories, whether participating in a cognitive evaluative process as empirical evidence or being the outcome of the process, are untainted, so to speak, by personal or social bias.

Socially-shaped strategies of scientific inquiry

Lacey’s account, however, allows for social values to enter science, although this penetration is not done through the use of the cognitive-values framework. Instead, social values penetrate scientific processes via strategies of scientific inquiry, whose elaboration is a major part of Lacey’s theory of science—and essential for the objectives of my thesis. A strategy for the pursuit of scientific knowledge is an intellectual track that defines a particular approach to the scientific understanding of phenomena, and sets the goals for which scientific inquiry can

84 Ibid. 61

85 In brief, the list of cognitive values that Lacey accepts (and argues for) are empirical adequacy, explanatory and unifying power, power to encapsulate possibilities, internal consistency, consonance, interpretative power, puzzle-solving power, and simplicity. Ibid. 28-30

86 This is the neutrality attribute of science, which ensures that theories do not make commitments to any value judgments, and are thus neutral to anyone’s value complex. Lacey 75

87 For an account of approach, Ibid. 21, 256. For a brief account of scientific understanding/inquiry, Ibid. 95, 100-1.
be pursued. Therefore, deployed strategies account for the direction of science, although they are not committed in advance to the acceptance of any particular scientific theory\textsuperscript{88} (as already explained, theory acceptance is solely contingent on considerations of empirical evidence and cognitive values).

Strategies of research (and, by extension, their related approaches) interact, in mutually reinforcing ways, with moral and social values that are deeply embedded and manifested in social institutions, especially those associated with science. In setting a direction for scientific investigation, strategies frame practices of inquiry, and as a result, the values to which they bear reinforcing relationships place constraints on the kinds of theories (or, rather, hypotheses) that science is geared to explore as candidates for possible acceptance.\textsuperscript{89} Likewise, they also constrain the kinds of pertinent empirical data that must accommodate (and be accommodated by) the selected theories.\textsuperscript{90} This fit between theories and empirical data concerns the idea—and a central cognitive value in Lacey’s list—of empirical adequacy,\textsuperscript{91} which characterizes the process of assessing hypotheses against empirical data in scientific inquiry.

Aside from whatever methods are followed in the (internal, value-free) processes of empirical adequacy, a host of outcomes is yielded that, in many essential ways, is determined by the approaches, strategies, and related social values that form the context of the scientific inquiry at hand. Thus, the emergence of an accepted theory constitutes the visible outcome of empirical

\textsuperscript{88} Lacey insists that “the levels of (and grounds for) strategy adoption and theory acceptance need to be clearly separated.” Ibid. 22

\textsuperscript{89} Ibid. 256

\textsuperscript{90} We could reasonably assume (although Lacey does not specify so) that these selected theories include candidate hypotheses and already accepted theories that can be consulted in this assessment process. Ibid. 92

\textsuperscript{91} Ibid. 58-9
adequacy in research, although there are also important hidden outcomes in the form of possibilities open to phenomena that the theory can grasp. These possibilities define the theory’s predictive power regarding phenomena observable (or detectable) in the future, and its capacity to explain them in advance.

**Materialist strategies of control in science**

To illustrate these central points of his theory, Lacey specifies that, within the modern, systematic empirical approach to scientific understanding, the dominant strategies in current scientific inquiry are the so-called materialist strategies. These aim to understand and represent phenomena in terms of a causal origin that is posited to consist of underlying structure, process, and law. Moreover, materialist strategies interact—in mutual reinforcement—with values of control, which are manifested in the human “capacity and desire to exercise control over natural objects.”

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92 The power to encapsulate possibilities is a cognitive value in Lacey’s list. Ibid. 60

93 For instance, the theory that stem cells have the potential to develop into any kind of cell and tissue entails the possibility of generating healthy brain cells. This phenomenon (which has yet to be fully corroborated) contains the possibility of replacing defective cellular brain areas that are responsible for the causes of Alzheimer’s disease. Therefore, it may be said that two of the (hidden) possibilities of the stem-cell theory are healthy-brain-cell generation and a cure for the said disorder (and, possibly, for many others).

94 Although this approach is (in principle) one among many, it is the one adopted by modern science, and is based on Baconian ideas of experimental method and scientific (empirical) inference. Lacey 4-5, 21

95 Materialist strategies are based on the Galilean metaphysical conception of the world viewed as “the spatio-temporal totality [of the ‘facts of nature’ that] is fully characterizable and explicable in terms of its underlying order.” Ibid. 2-3

96 Ibid. 21
As a result of their goals and interacting social values, materialist strategies constrain the theories that science entertains by causing it to include only those theories that view and represent phenomena as being generated from this “underlying order.” In addition, the empirical data they select as pertinent to these theories represent phenomena in *quantitative* terms, and “in abstraction from the human and social contexts of the investigation.” In this way, the possibilities open to phenomena that can be grasped by accepted materialist theories bear no connection with, say, the social context (i.e. social relations and social order) in which the phenomena are (or may be) observed.

When leading social institutions (largely, but not exclusively, institutions of science) are dominated by materialist strategies of control, *control* becomes the principal social value that infuses most social practices. The manifestation of the value of control is most evident in the production of technological objects, whose widespread use essentially determines the production process in most social institutions and practices. Because technology is typically viewed outside its social context, only its material products and the processes underlying their production receive attention, whereas the human agency, values, and interests that animate the social institutions and practices associated with technology are largely ignored.

Understandings of the world gained under materialist strategies of control have important implications on the possibilities and structuring of human lives, such as are manifested in the structures, goals, and consequences of social practices in, say, employment, education, health care, or clinical research. To be certain, socio-moral, cultural, and political issues are articulated

97 Ibid.
98 Ibid. 203
99 The ubiquitous computer technology illustrates the point.
in the context of these implications and, generally, are addressed by social studies, but not by the

dominant institutions (i.e. of business, science, technology, etc.) that have the greatest impact on
people’s lives.

Even if materialist understandings are to be retained for offering valuable knowledge of
the world, one might still challenge the endorsement of values of control as leading to policies
and social structures that diminish the possibilities of other forms of human flourishing (however
defined). Lacey is keen on acknowledging the desirability of alternative value complexes, and
points out that the adoption of particular sets of values is a moral—and, I would add, political—
question. This assertion underscores Lacey’s conception of the social dependence and shaping
of scientific inquiry and scientific beliefs.

Longino’s feminist account of scientific inquiry

Let us now turn to Helen Longino’s account of scientific inquiry Essential Tensions—
Phase Two: Feminist, Philosophical, and Social Studies of Science. Here, we encounter an
approach embedded in feminist values, which are manifested in the fact that all scientific
processes (including the internal cognitive ones) are viewed and analyzed in a context of
intentionality, intersubjective practices, and social values. Contrary to materialist strategies of
test, which reserve no role for intentional categories in the generation of scientific beliefs, the
feminist approach accords human agency a central place in this process (and in belief formation,
in general), and rejects the “dichotomizing of the social and the cognitive.”

100 Not all value complexes are compatible with materialist strategies (e.g. feminist approach).
Ibid. 205
101 Longino
102 Ibid. 260
In addition, if the task of the feminist proposal is to reveal “the ideological dimension of knowledge construction” and expose its structures of control, Longino’s theory accomplishes this goal by showing the pervasiveness and shaping of scientific inquiry by social values. Longino will arrive at this conclusion through the elucidation of scientific practices in an empiricist analytical context, which nonetheless rejects the positivist epistemology of scientific inquiry and knowledge. To buttress her claim of the social construction of scientific beliefs, Longino also endorses a notion of objectivity. Besides being a foundational concept in her theory of scientific inquiry, objectivity provides Longino the possibility of a tactical maneuver toward enabling (and encouraging) feminist critique to penetrate empiricist discussions of science. The intention of joining such considerations is to broaden them with alternative feminist perspectives.

Social values as the backdrop of cognitive processes and objectivity in science

The feminist theory of scientific inquiry offered here is constructed from what Longino calls a contextualist empiricist perspective. Let us first see how she establishes the empiricist part of it. Making sure to reject the positivist position as untenable, Longino adopts a core principle of empiricism that considers “experiential or observational data [as] the only legitimate bases of theory and hypothesis validation in the natural sciences.” She then proceeds to

103 Ibid. 257
104 The positivist epistemology of science claims a veridical representation of the world by scientific theory.
105 This suggestion points to the typical feminist, off-hand rejection of objectivity as being an epistemological construct in the service of androcentric ideologies of control. Ibid. 260-1
106 104n
107 Longino 261
articulate the meaning of *experiential inference*,\(^{108}\) as she terms the relations (of inference) between empirical data and the hypotheses to be assessed.

These relations unfold in the course of the cognitive processes of scientific inquiry that account for the acceptance (or rejection) of hypotheses. Relations of inference essentially constitute a set of *background assumptions* about what may count as evidence for the (non)selection of a hypothesis, when one’s tools are a specific set of data and certain already available theories. These assumptions, however, are simultaneously the means of letting social values and ideology be expressed in the context of scientific inquiry. Whereas Lacey would allow for only value-free cognitive criteria to guide the internal cognitive reasoning that determines evidence, Longino views this stage as manifesting social values that “become subtly inscribed in theories, hypotheses, and models defining research programs.”\(^{109}\) It is this context of social values that characterizes Longino’s empiricism as contextual.

Moreover, Longino’s social construal of scientific inquiry is based on her thesis of *social knowledge*, arguing that scientific knowledge is the fruit of cooperative efforts of people acting within communities of knowledge, and not the work of isolated individuals.\(^{110}\) This view regards *observation* and *reasoning*—the pre-eminent cognitive practices of scientific inquiry—as a collective project with two basic features: First, details of experiments are conveyed so as to make their *intersubjective* verification possible, and second, there is *consensus* among

\(^{108}\) This is a category that comes close to Lacey’s *empirical adequacy*.

\(^{109}\) Longino 263

\(^{110}\) Ibid. 263-4
researchers about “the ontological and organizational commitments of a [scientific] model or theory.”

This social, interactive, and dialectical aspect of scientific inquiry ensures that the criteria for hypothesis acceptance (or rejection) are “nonarbitrary and nonsubjective (or nonidiosyncratic).” They are thus objective, in the sense that background assumptions are not shaped by subjective (idiosyncractic and arbitrary) preference, insofar as observation and reasoning in scientific inquiry constitute a social enterprise. Therefore, Longino frames objectivity in terms of the social practices of inquiry, which function as a safety valve, so to speak, against the undue penetration of science by arbitrary choices. This elucidation of the internal structure of objectivity is, at the same time, consistent with the claim that science, in its internal reasoning processes, is pervaded and shaped by social values.

Viewing clinical research as a structure of destabilized scientific beliefs

Although Lacey’s and Longino’s theories of scientific inquiry differ radically regarding the phase of inquiry whereby social values enter the realm of science, they find common ground in recognizing the role of social values in the formation of scientific beliefs and conceptualizations. Their epistemological analyses of belief-gaining practices—exemplified here in the context of science—point to the social (and cultural) mutability of conceptions that are crucial in reflecting about biomedicine, clinical research, and their ethical implications.

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111 Ibid. 264

112 Ibid. 261

113 Observation includes the intersubjective verifiability of experiments (or experience), and reasoning involves scientists’ consensus on essential features of accepted theories, as already mentioned.

114 In this sense, Longino’s objectivity shares elements with Lacey’s impartiality and neutrality, although each of these concepts is different.
Following Lacey and Longino, we will proceed from now on to regard the concepts defining the structures and goals of clinical research—and its ethics—as unfixed, socially constructed, and historically mutable. The rest of this chapter will explore conceptualizations of health, disease, wellbeing, and the body—the main constituents of the conceptual basis of clinical research (and biomedicine)—from three analytical viewpoints: a socio-economic perspective that looks into health care resource allocation, a cultural context that is more specific to the U.S. (but one that we may call “Western”), and a technological context that views medical technology as a tool for controlling human physiology. Finally, from the perspective of technology, we will highlight the most basic concepts and beliefs that have been utilized in developing the structural features of clinical research (i.e. the randomized clinical trial) in the context of medicine’s scientific project.

The primary concepts of health and disease from a socio-economic perspective

In the socio-economic context, various notions of health with a social and economic significance constitute beliefs whose embedded values can differ radically across social groups or geographical borders. In the context of the U.S. health care system (which operates under the assumption of scarcity in resources), health is viewed as some kind of (social or individual) good, conceptualized within a variety of beliefs that articulate views about health care resource allocation—a political and ethical issue of substantial controversy. Two main rival theories approach this question, and both base their positions on notions of social rights and obligations, which they, nonetheless, define differently.

Thus, based on certain beliefs about health, and health care, as social goods, an egalitarian view argues that health care consists (in part) of needs that are fundamental to human
living because their fulfillment determines the maintenance of “normal species functioning.”\textsuperscript{115} In turn, the degree to which this functioning is sustained determines the “range of opportunity open to an individual” in society.\textsuperscript{116}

The connection of health care (and by extension, health) to the social structure of opportunity leads to an analysis of health care resource allocation in terms of a theory of distributive justice, in the context of which health care is defined in terms of basic human needs, and justice is viewed as fairness.\textsuperscript{117} The theory then concludes that, because of the especially vital status of health care (and health), each and every individual has the right to benefit from health care services.\textsuperscript{118}

On the other hand, a rival approach of libertarian bent argues that the only acceptable right is that of owning, and being in control of, one’s property, including the monetary funds that are used for the procurement of health care. Providing that the individual takes the responsibility to assume relevant costs through personal funds or appropriate insurance plans, he/she has the right to obtain the health care services of his/her preference, which may extend to better than basic, and even to luxury, care.\textsuperscript{119}

This approach also argues that because health care resources are created, and thereby already owned, by those who can fund them (and not by the state or the entire society), the

\textsuperscript{115} Daniels 320

\textsuperscript{116} Ibid.

\textsuperscript{117} Daniels proposes this analysis based on John Rawls’s conception of justice as fairness, although his account does not presuppose the acceptability of Rawls’s theory. Daniels 331

\textsuperscript{118} At least those services that provide the things necessary for the sort of functional organization that is defined—by a biological model of health and disease—as normal and typical of the human species. Daniels 326-9

\textsuperscript{119} Engelhardt 403 (1996)
economically disadvantaged ought not to make moral claims on resources that, according to the theory, are the private property of others.\textsuperscript{120} Moreover, as there is no specific understanding of \textit{beneficence} and \textit{justice} that is commonly and collectively upheld in a culturally plural society, there is no single moral vision of health care (and health) either. In this regard, claims for an all-encompassing health care system are ethically unwarranted.\textsuperscript{121}

\textbf{Egalitarian and libertarian conceptions of health and wellbeing}

Two different and interesting conceptualizations of health and wellbeing emerge from these rival approaches. For one thing, in seeking to underpin the distribution of health care resources on a needs-based theory of justice, the egalitarian proposal requires some \textit{stable} concept of needs, which it defines by \textit{objective}, and not \textit{subjective}, criteria.\textsuperscript{122} In other words, the argument’s task is to identify a class of things, or goods, that would be both \textit{ascriptible} to, and \textit{important} for, every human being, in the sense of being \textit{certainly needed} for some fundamental and objectively defined reason.

Indeed, this reason, according to the argument, is the \textit{vital} importance of these things (or needs) in maintaining the functional organization that is intrinsic to humans as a biological \textit{species}.\textsuperscript{123} Therefore, these types of needs reveal a meaning of health and wellbeing that is grounded in a naturalistic kind of functioning and its underlying structure, both of which are

\begin{itemize}
  \item \textsuperscript{120} Ibid. 379
  \item \textsuperscript{121} Ibid. 375-6
  \item \textsuperscript{122} In this approach, subjective criteria use individuals’ own evaluation of their situation, including their measure of their (dis)satisfaction, in determining the significance of claims that are relevant to the handling of particular resources. Conversely, objective criteria appeal to a measure of importance of relevant claims, irrespective of individuals’ strength of preference or value judgments. The egalitarian approach claims to rely solely on a selective scale of objective criteria of human wellbeing, based on what is \textit{indeed needed} and not simply desired. Daniels 323-4
\end{itemize}
peculiar to human life at the species level. Health, therefore, emerges as a natural kind of good, in which all humans should partake on account of their nature as biological beings.

Moreover, the argument holds that the failure to fulfill these needs diminishes the human ability to achieve goals, tasks, and conceptions of the good that define understandings of a meaningful life in a particular social context. Therefore, these needs (which are tightly connected with health and wellbeing) are indirectly defined in terms of social (and moral) values that characterize possibilities of meaningful human existence in a given society. This conceptualization points to a normative, socially- and culturally-defined notion of health and wellbeing that can be in tension with an understanding that is biologically framed.

Because each of these conceptions points to a different (kind of) source of meaning for health and wellbeing (i.e. natural and social sources), the challenge for the theory is to identify a conceptual space, whereby the somatic merges with the social in the sense of reconciling natural needs of health, and health care, with social ones. Yet, in the context of a culturally diverse and constantly changing social world, conceptions of a meaningful life differ, become adjusted to new conditions as they develop, and impose differing requirements for health and somatic (as well as mental) wellbeing. For all these reasons, trying to delineate even a minimum (qualitative) standard of health, and health care, becomes extremely problematic.

Yet, the theory also points to a conception of health viewed as a public type of good, to which all individuals are entitled because of its special status as a life-sustaining factor (at both the individual and collective level). Therefore, any resources that may permit the preservation, restoration, and possibility of widespread sharing of this good should be managed and regulated by public institutions which, in a democratic society, have a popular mandate. In this regard,

123 Daniels 325
whether biologically- or socially-defined (or both), health and wellbeing become quasi-political concepts, reflecting moral understandings of the good in the public sphere.

On the other hand, the libertarian approach seems to consider health care, and by extension health itself, as consumer goods, whose distribution should be entirely left to market forces, as the state would be committing a forcible act if it should undertake the allocation of health/health care resources on its own. Since the procurement of means that could ensure a measure of health is contingent on private property, health emerges as a private economic concept of restricted social relevance.

Primary concepts of health, disease, wellbeing, and body in a cultural context

Let us now explore some conceptualizations of health, disease, wellbeing, and the body from a cultural viewpoint, and specifically (although not exclusively), in the context of the general U.S./Western culture. Categories of race, ethnicity, gender, age, sexuality, and economic class have historically been at play in the formation of social and medical conceptions of body/mind and health/disease. Numerous socially-constructed, essentialist preconceptions of a “normal” bodily constitution and health status have cast particular social groups as lacking (or, at least, as being “different”) in physical and mental vigor, relative to others that are taken to represent the norm. Most importantly, such beliefs have greatly informed practices of clinical medicine and research with, in certain cases, devastating social consequences.

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124 It would be interesting to see the theory’s position regarding the state’s authority to enforce the law and prevent criminal acts, if in fact no societal agreement on justice and beneficence could be assumed.

125 Typically embodied by the white (and preferably of relative youth) middle class, Anglo-Saxon male.
Health and disease from a race viewpoint: Tuskegee and BiDil

Already briefly explained in the previous chapter, the Tuskegee syphilis study presents a classic illustration of racially-defined medical attitudes and practices reflecting racist conceptions of body and mind, health and disease. These conceptions were embedded in beliefs of racial superiority/inferiority, which included essentialist representations of the Negro body, imagined to be frail and susceptible to disease. Indeed, the perception of black susceptibility had developed into a monstrously sensational anticipation of the imminent extinction of the black race as a result of natural selection. Likewise, the Negro mind was believed to be irrational, naturally desiring promiscuity (especially when male), and a lifestyle of illiteracy and poverty. The fact that these beliefs were socio-moral stereotypes about blacks, and simply reflected the dominant white culture’s moral values on sexuality, education, and economic status, made no difference in the post-abolition American South.

At the time of its conduct, the study was presumed to exemplify unbiased empirical science, although in a rather perverse way. Although the study initially aimed at finding some race-specific syphilis effects, its goals were interim modified, and the study was geared toward observing the natural history of the disease, as subjects were available and vulnerable. The researchers took great pains to accomplish this goal by following the unfolding of the disease to

126 Chapter 1 17

127 For an account of the physical constitution of the Negro race [sic], used as an argument to justify slavery, see Cartwright 305-25.

128 In addressing this issue, DuBois shows how vital statistics on the races were made inaccurate in order to have blacks appear more susceptible to disease. DuBois 31

129 Brandt 16-7

130 “The stated purpose of the [study] was to compare health and longevity of an untreated syphilis population with an otherwise similar nonsyphilitic population.” McDonald 203
the death of their subjects, and even beyond that point, through the meticulous conduct of well-planned autopsies.\textsuperscript{131} From a technical viewpoint, research procedures were thought to be scientific and unbiased at the time of the study’s conduct,\textsuperscript{132} and the study seems to have contributed important biological and medical knowledge.\textsuperscript{133}

Yet, no ethical dilemmas were entertained about not offering therapy to patients,\textsuperscript{134} as the funds for the treatment of African Americans had been withdrawn due to the economic effects of the Great Depression—a fact that had prompted the study as an offered “ready-made situation” in the first place.\textsuperscript{135} Why these funds should have been withdrawn at all, and how black people could access medical care with no resources of their own, was no matter of ethical concern, but simply a fact of life. In this sense, the study was not thought to deprive its subjects of anything they could otherwise have had; their deception about the goals of the study was simply a necessary means to an important (scientific) end.

This stance toward the predicament of people of color, which seems to border on both naiveté and wickedness, reveals the researchers’ unmistakable internalization of the widespread racist attitudes of their place and time. Having allowed race, a socially constructed category, to become the leading factor in a naturalistic equation that sought to elucidate the natural phenomenon of a disease, investigators approached their judgments as reflecting seemingly

\textsuperscript{131} Jones 132

\textsuperscript{132} Later critics suggested that important gaps in the study, such as the absence of a study protocol and a comprehensive plan, greatly diminished the methodological merits of this research. Benedek 229-32

\textsuperscript{133} Ibid. 232-3; McDonald 206-10

\textsuperscript{134} Even when penicillin became available to the broader population during the last half of the study’s duration. Heller 116-8

\textsuperscript{135} Lederer 266
empirical facts about the effects of race on physical, mental, and sexual health. Therefore, we see how the socially constructed category of race informs conceptions of physical and mental health, disease, and the body in the case of the Tuskegee study, and becomes a marker for some perceived “natural” or genetic characteristic.

A similar case of introducing race into a biological/genetic context of evaluating a candidate therapy was presented recently. The controversial drug known as “BiDil,” developed by the corporation NitroMed, was granted FDA approval in 2005 for being the “only cardiovascular drug recognized by AHA [American Heart Association] for dramatically improving survival in African American heart failure patients.” Although two previous clinical trials on patients from the general population had failed to show any health benefit, resulting in the rejection of BiDil in 1997, this time FDA welcomed the newly approved drug as “a step toward the promise of personalized medicine.”

The difference between the two instances was a new three-year study that involved 1,050 heart failure “self-identified black” patients (as the FDA news release was careful to note more than once), whereby BiDil was claimed to significantly reduce mortality and morbidity rates (i.e. improvement in survival, first heart-failure-related hospitalization, and quality of life). Although the new study data that prompted NitroMed’s re-submission of the BiDil candidacy for FDA approval reflected only “preliminary” results, the study was not able to establish the

136 A combination of two older generic drugs, hydralazine and isosorbide dinitrate
137 This is how NitroMed referred to the results of a study of BiDil efficacy that eventually led the drug’s FDA approval. NitroMed
138 Kimberley
139 U.S. Food and Drug Administration, FDA News
140 Ibid.
biochemical mechanisms through which the alleged health benefit was induced.\textsuperscript{141} Now, with a patent based solely on the African American Heart Failure Trial (A-HeFT), and protected until 2020 as opposed to a general-population-based patent that would expire in 2007,\textsuperscript{142} NitroMed is looking at a one-billion-dollar market opportunity by urging thousands of black patients to take BiDil.\textsuperscript{143}

Meanwhile, no good evidence exists as to why BiDil should be more effective than any other drug tested on black populations, as study subjects were exclusively African American, and no comparison population (presumably of European, or Asian, or other descent) was enrolled to allow for comparative statistical data. Yet, Dr. Yancy, a BiDil study author, seemed to be convinced that “heart disease is the leading cause of death in the African-American community,” and the purpose of this study was to “find the best treatment for a disease that happens to be in a specific population.”\textsuperscript{144}

This statement flagrantly overlooks the fact that heart failure is the leading cause of death in the general population regardless of race or ethnic origin, and the absence of meaningful comparison. Moreover, any race-related effectiveness of BiDil (with regard to African Americans, in this case) can be understood only if a high incidence of heart disease and related death is shown to be connected with racially-defined genetic characteristics (of African Americans).

\textsuperscript{141} FDA Advisory Committee

\textsuperscript{142} Kimberley

\textsuperscript{143} FDA Advisory Committee

\textsuperscript{144} Fouad
These connections are extremely difficult (if impossible) to establish because of the tremendous genetic variation that is present among people of African descent the world over.\footnote{Duster 1050-1} Moreover, there seems to be a rush to medicalize race and ethnicity in explaining the incidence of cardiovascular disorders in African Americans without examining the possibility of dietary practices and socio-economic disparities in health care across “races,” rather than genetic factors, being at the root of the disorders.

At the beginning of the thesis, we took a glimpse of the promise that the new era in drug development holds thanks to human genomic knowledge. Indeed, if effective therapies can be safely delivered to “special subpopulations that have some functional genetics markers,”\footnote{Ibid. 1051} the drug industry should do so for all populations with those markers, irrespective of ancestry and with no reference to racial categories. Using “race” as a genetic marker reflected in skin color or other such phenotypes increases the likelihood of fallacy in scientific concreteness, and worse yet, in the social tendency to reify race through a new “biological reinscription of the concept.”\footnote{Ibid.}

Health, disease, and body from gender and sexuality viewpoints

Considerations of gender and sexuality have also influenced conceptions of health and disease. For one thing, women’s special health needs on account of their different physiology have historically been met with much less medical attention than men’s. This neglect, even to this day, is exemplified in the relatively small scale of clinical research devoted to new therapies for women, whereas most clinical trials are limited to only male subjects. Most new therapies

\footnote{Duster 1050-1}
\footnote{Ibid. 1051}
\footnote{Ibid.}
for women (and even children) are generated through extrapolation from male subjects’ research data.\footnote{Luna 260-1}

Moreover, the link between sexuality and conceptions of health and disease has been most strongly manifested in the association of homosexuality and HIV/AIDS. At its peak in the 1980s, when the first devastating symptoms of AIDS were observed among thousands of gay men, this association quickly led to the term “gay cancer,” and the portrayal of the disease as evidence of gay men’s physical vulnerability. This was thought to be the result of their specific “nature,” which drove them to sexual practices that were abhorrent from both a naturalistic and moral perspective.\footnote{Cantwell} It took several years of research, and a full-blown epidemic across male and female heterosexual populations on a global scale, to realize that the disease was the result of a certain viral entity whose transmission was due, not to a specific sexual orientation, but several factors, one of which was (“unprotected”) sex.\footnote{HIV-contaminated blood transfusions and perinatal (mother-to-infant) transmission have been the usual factors other than sex.}

There is an essentialist connection between homosexuality and AIDS. This means that “AIDS” becomes a signifier of some perceived innate, sexually defined characteristic of specific bodies (the bodies of homosexuals), which is imagined to be unchangeable—part of the “essence” of these bodies. This essentialism points to \textit{psychological} and \textit{ethical} conceptualizations of disease that have significant social implications. In her study of how illness has traditionally been used as a metaphor, Susan Sontag argued that metaphorical interpretations of disease distort natural phenomena, such as the symptoms/physical expression...
of diseases (which medicine should reveal for what they are),\textsuperscript{151} and create an emotionally charged atmosphere that, as a rule, contributes to the stigmatization and isolation of the sufferer.\textsuperscript{152}

Sontag has argued that moralistic conceptions of disease are reflected in the metaphor of disease as punishment, and point to the existence of an objective moral being that the sufferer cannot (apparently) possess; one’s disease and suffering are proof enough of one’s innate immorality.\textsuperscript{153} Although this view seems to be extreme in the case of, say, smokers with lung cancer (who are not normally treated as “responsible” for their illness), gay AIDS patients have, for the most part, been approached with suspicion, hostility, and contempt, as society typically perceives them to be immoral, and rightly punished through physical suffering.

Such conceptions of disease often victimize and cut off patients from their societal context, and make them feel culpable and, in a very real sense, socially vulnerable. AIDS, which is connected to sex (a taboo matter) and homophobia, points to conceptions of illness and disease as containing intense \textit{moral} meanings (i.e. condemnation of individual character and a justly ravaged permissive society), as well as \textit{psychological} ones (i.e. guilt on the part of the sufferer).

As Paula Treichler has argued, the social dimensions of disease can be much more widespread than the biological categories in which diseases can be understood, and HIV/AIDS seems to be, in Treichler’s words, mostly an \textit{epidemic of meanings} or \textit{signification}.\textsuperscript{154} Indeed, so deeply pervasive are the socio-moral conceptualizations of AIDS that it is hard to dismiss them.

\textsuperscript{151} Sontag 3
\textsuperscript{152} Ibid. 6
\textsuperscript{153} Ibid. 45
\textsuperscript{154} Treichler 11
as irrational myths. To the contrary, such constructions of disease are worth studying, because an understanding of how AIDS semantics works in the social imaginary points to the ways they have helped to shape our societal norms.\textsuperscript{155}

In the broader context of culture, sexuality- and youth-based normative conceptualizations of the body have particular currency, as is evident from contemporary popular discourse (disseminated through text, sound, visual images and the like). Thus, specific states of bodily fitness and beauty depicted as valued instances of wellbeing are designated as “sexy” and young. The cultural tendency to favor this youth-and-sex combination is not new, but a historically persisting trend. Yet, what is rather new today is the trend’s sizeable and particularly aggressive promotion by means of resources that are liberally utilized in every area of production, ranging from fashion, to all forms of art, to technology and science, to education and the entertainment industry.

Thus, types of human behavior and lifestyle, particularly ones that are connected with the consumption of specified products, are vigorously publicized as leading to the acquisition of a (socially constructed and) valued kind of physique, health status, and sexual charisma. Given that an ideal of eternal sexual youth is not feasible, these proposals—if appropriately powered by the media apparatus—can lead consumers to a ceaseless pursuit of an unattainable dream, which occasionally finds temporary justification in the results of, say, physical exercise programs, dietary and cosmetic products, and physical enhancement surgical procedures. By producing normative conceptions of health, wellbeing, body, and bodily aesthetics, this socio-cultural and economically-shaped youth-and-sex ideal influences individual senses of self, and shapes societal norms relative to these concepts.

\textsuperscript{155} Ibid. 13, 15
The primary concepts in a culture of medical technology

A last exploration of the basic concepts of health and disease, body and wellbeing, can be carried out in the context of medical technology and its uses. Having been a tool for transforming—indeed, revolutionizing—medical practices, this technology can be viewed as reflecting, and (re)shaping, social, cultural, and moral understandings of these concepts. These notions, in turn, have a bearing on conceptions of human life and personhood (matters that still remain controversial, to be sure), which are related to the practices and ethics of clinical research.

The tremendous growth of medical technology, both in its scope of application and depth of sophistication, has rendered it ubiquitous in every area of medical activity. Its main objective is to facilitate and expand diagnostic and therapeutic possibilities in both medical practice and research, in order that an increasingly more rational and efficient management of the body’s physiology may be achieved. Yet, in line with dominant social values of control, medical technologies seem to have radically transformed these possibilities in many areas of therapy. A technological imperative has settled in the context of medical practice that relentlessly requires more procedures utilizing ever more invasive technical means.\textsuperscript{156} As a result, what were once believed to be the natural limits of body processes have now been pushed to a level whereby physiological functions can be regulated at will.

The management of the body’s physiology through technology is more commonly manifested in regulating illness (understood as a cluster of symptoms that betray some kind and degree of somatic impairment), while a treatment is being applied for the cure of the disease.\textsuperscript{157}

\textsuperscript{156} Kaufman 27

\textsuperscript{157} The distinction between illness and disease has been explained on p. 40-1 (68n).
The immediate effort to normalize symptoms in the sick body reveals a concept of illness (and by extension, of disease) that is understood (and usually experienced by the ill) as limiting the body’s range of “normal” functions. Therefore, illness and disease are often thought of as limitations, or undue constraints, to a somatic (anatomical and/or physiological) concept of individual freedom.

If the therapeutic application of medical technology strives to (re)establish somatic autonomy, it also seems to modify it in ambiguous ways. Contemporary medicine’s technological imperative constitutes a discourse in which medical choices are framed and dilemmas are worked out. A conception of appropriate care, embodied in maximum technological intervention, narrows (rather than expands) physicians’ field of possibilities and moral options.158

This fact is more visible in the context of pregnancy, childbirth, and death. Traditionally regarded as natural, and not readily amenable to human control, these processes have become highly medicalized, as they are increasingly administered by technology. When occurring “naturally,” pregnancy and childbirth are routinely treated, and monitored by technology, as quasi-illnesses (rendering thus the old art of midwifery virtually obsolete). Yet, technological innovations in the area of human fertility and reproduction have created a new level of intervention, whereby an industry of infertility may readily intersect with eugenic aspirations and approaches. What is revealed by reproductive technologies is a concept of the body that is malleable at the genetic cellular (if not molecular) level, and whose somatic, mental, and even psychological attributes are the target, and outcome, of individual rational choice.

158 Kaufman 27
As for the process of dying (which, in reality, corresponds to the very processes of living and aging that gradually lead to death), it is treated as a condition to be indefinitely postponed, or at least regulated at human will, through the use of heroic and extraordinary technologies.\textsuperscript{159}

More than that, American society and culture, aided by the law and the necessary technical capacities, create a cultural and legal environment that vehemently resists the idea, and the fact, of human mortality. Frustration over the excesses in applying medical technology, whose application is often seen as obstructing more than aiding the natural processes of dying, has led to activism for specific legislation in response to a perceived threat of “life without dignity” being imposed by medicine and the courts. The result has been the generation of legal technologies, such as \textit{living wills} and \textit{advance directives}, for securing societal and medical non-interference with individuals’ end-of-life decisions.

\textbf{Brain death and its medical, ethical, and social implications}

It appears, therefore, that life and death are no longer clear-cut states of being, but conditions to be medically and legally (re)defined in an effort to comprehend—and, at times, to accommodate—biological outcomes of medical technology. This ambiguity creates a conceptual and moral tension in medical approaches to death, and generates serious ethical dilemmas. For instance, the concept of \textit{brain death} has been the epitome of a serious medical, legal, and philosophical controversy in the last few decades with respect to medically defining death, and confirming it by appropriate clinical criteria and diagnostic means.

\textsuperscript{159} This point is reminiscent of Terri Schiavo’s death process, a Floridian who was “allowed” to die on 31 March 2005 following the removal of her feeding tube. Schiavo had been in a vegetative state, and clinically diagnosed as cerebrally dead, for more than a decade. Her case was heavily politicized, and perhaps the most legally contested, instance of bioethical concern, especially as regards the medical, ethical, and legal implications of defining brain death in recent decades.
These problems arose in the 1950s when critical care technology was applied to treat severe brain damage (in cases of head trauma, deep coma, or cardiopulmonary arrest), and comatose patients progressively entered a state of physiological dissociation, whereby, in spite of an irreversibly inactive brain, they could be kept alive thanks to life-support technology and to well-functioning systemic organs. Such phenomena led to a re-definition of death in terms of cerebral, as opposed to respiratory/circulatory, functioning, which then made it necessary to delineate specific clinical and laboratory indicants reflecting unequivocally the transition from an impaired to a dead brain.

A key issue in defining brain death has been to specify whether all, or what part(s), of the brain must be irreparably inactive so that a brain (and hence a patient) might be considered dead. (An equally significant issue is that of the kinds of diagnostic procedures to be used in confirming brain death.) Medical disagreements on these matters have been amplified by the terribly controversial concern of organ transplantation.

As transplants must be promptly removed from a body, a brain-based definition of death would have to be such that allows for the timely harvest of organs, while leaving no doubt about the presence of death (however it may be defined). To complicate matters, any medical consensus about such a definition would have to resonate with the broader public, so that the medical profession might avoid accusations of murder or organ stealing.

Through the years, and on the basis of such complex considerations, more than one definition of brain death has been proposed. Among them is the one developed by the President’s Commission in 1981, which accepts brain death as a result of an “irreversible

\[\text{Plum 34-5}\]

\[\text{Pernick 9}\]
structural…damage that has permanently destroyed all functional brain activity, including that of the brain stem.”\textsuperscript{162} However, based on the medical belief that the brainstem holds the critical nerve centers that make brain life possible,\textsuperscript{163} a different definition was advanced, and concentrated on signs that can unequivocally show irreparable inactivity of the brainstem, as opposed to loss of function of the entire brain.\textsuperscript{164} These definitions are only a small part of the broader medical, legal, and ethical discussions of cerebral criteria of death.

The issue of defining and confirming brain death is still a matter of unresolved controversy.\textsuperscript{165} Moreover, according to certain views, the basic meaning of this contestation is reflected in the fact that “warm, breathing, pulsating human beings are not given further medical support [and]...their hearts and other organs can be cut out of their bodies and given to strangers.”\textsuperscript{166} An ethical implication of this statement is the exclusion of human beings from the moral community\textsuperscript{167} as soon as they are diagnosed to be cerebrally dead (and, by extension, dead in a general sense).

If this realization is accepted in the context of the medical profession (at least), it seems to reflect the idea that there exists a physical locus of human personhood—whether the entire brain or the brainstem, in this case. Moreover, the issue of brain death combined with that of organ transplantation reveals a dominant utilitarian understanding of the human body, which can

\textsuperscript{162} President’s Commission

\textsuperscript{163} Plum 37-8

\textsuperscript{164} Ibid. 37

\textsuperscript{165} The Schiavo case has been extremely poignant in this regard. 161n

\textsuperscript{166} Singer 293

\textsuperscript{167} Ibid.
be used for purposes that surpass the limits of its physical life, and toward enhancing the life of other bodies.

In a sense, this utilitarian approach is familiar in the context of clinical research, whereby one’s body becomes the biological substratum for testing new therapeutic substances that may respond to the needs of the bodies of (mainly) future patients. The philosophical challenge in both the cases of brain death/organ transplantation and clinical research is to (re)establish the human being back to the moral community via an ethics that goes beyond ontological considerations of human personhood, and is more reflective of the moral value of an exchange between society and the individual that is rooted in reciprocity, generosity, and respect.

Elements of modern clinical trials: randomization and blinding

In the context of exploring concepts of technology connected with medicine and clinical research, it would be purposeful to look into the development of the experimental project of medicine, and thus at some basic concepts and principles/beliefs that constitute the scientific/technical foundations of clinical research. It should be noted that medicine as a scientific-rationalist enterprise—as opposed to the empirical art of healing it had been for most of its history—had reconceived its central goal of restoring human health. According to new theories of disease, medicine’s central task was to identify pathogenic agents invading the body and devise ways to neutralize them.

The most significant consequence of adopting the scientific model in medicine was the modern conception of the medical experiment. Just as a natural science experiment aims at the \textit{in vitro} replication of natural phenomena in a laboratory setting (with the intention of enhancing the researcher’s capacity of observation and data collection), the medical experiment aims at “reproducing” whatever “natural” processes would occur within a sick body, if this body
chanced upon a therapeutic substance, or another form of treatment, under “natural conditions.” As we may justifiably believe that the probabilities of this occurrence (let alone of its deliberate observation) are extremely diminished, the medical experiment is designed to bring about, and enable the observation and measurement, of the effects of proposed treatments on suffering patients under controlled conditions (i.e. in a clinical setting).

In emulating the scientific method for the testing of medical therapies, the development and application of statistical analysis (initiated in natural science) became a crucial factor. In using statistical methods, the crux of the matter was the possibility of making important inferences with respect to populations, as opposed to isolated individuals. In the context of testing candidate therapies for efficacy, a statistical approach to human experimentation meant that the degree of efficacy of tested therapies could be better assessed if test results could be shown to be significant, given the size of the tested population.168

Moreover, the statistical method would be most productive in answering questions of therapy efficacy if it were applied in comparing medical outcomes on populations, in which at least one important variable of the study hypothesis could be controlled. The most basic variable was, obviously, the presence (or absence) of the therapy under consideration, and consequently, the populations to be tested were to be treated and untreated groups of patients.

To maximize the scientific rigor of these comparisons, experiments would also have to allow the laws of chance to enter their procedures by randomly assigning subjects to treatment and control groups (including those of inert placebo), so that the differences in outcomes could be compared. This idea generated the technology of trial randomization, conceived to enhance the rigor of comparisons and the validity of experimental results. Randomization had to be
impartial, in the sense that no human desire or value could enter the scientific equation of the experiment. Thus, information regarding which of the participating patients were (or were not) receiving therapy, or which kind of therapy they received if the experiment had been designed to test the efficacy of two or more different treatments, was not to be disclosed to patients, and sometimes, even to researchers.

This precaution, known as a trial’s *single-blinding* and *double-blinding* respectively, as well as the randomization technique, constitute basic principles in the design of medical experiments that became known as Randomized Controlled Trials (RCTs). First tried in epidemiological studies in 1920s-30s, RCTs remain, to this day, the quintessential method in assessing therapy efficacy, including, not only drug treatments, but even surgical operations. Their appeal and acceptability as scientific projects is based on features (e.g. impartial observation, data collection, and data interpretation, relative control of variables, etc.) that partake of the conceptual structure of the modern scientific method, as it has been described in previous pages.

Yet, we have also seen that scientific processes, engendering scientific beliefs (and vice versa), are not exempt from social value. Moreover, whatever its claims of scientific acceptability, human experimentation (in the form of clinical research) must enter this multifarious conceptual, socio-cultural, ethical, legal, and political context that we have explored in this chapter. In this multiple-layered environment, often confusing and burdened by conflicts of interest among its various constituents, clinical research must perform medicine’s bid to generate scientific knowledge by experimenting on human bodies.

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168 For a history of the statistical conception of medicine in testing the efficacy of therapies, see Fisher 3-6.
At the same time, medical practice, as a compassionate art of healing, is called to honor its centuries-old commitment to alleviating human suffering connected with issues of health. The extent to which these two missions of medicine are (in)compatible depends not only on the methodologies of research (which can be assumed to be constrained by the formal exigencies of the scientific project), but also on the theoretical precepts, and even the rhetorical construction, of an ethics that may warrant the social and moral acceptability of clinical research.

In this chapter, we have conducted a microscopic examination of clinical research, and more specifically with regard to its conceptual foundations at the level of research regulation, the epistemology of science, the conceptualization of research as a scientific project, and the structure of RCTs. We have also looked at a deeper conceptual basis, which we mainly defined in terms of notions of health and disease, human wellbeing, and the body, whose multiple meanings we explored in the contexts of science and technology, society, culture, and economy.

We thus discovered that these concepts are shaped by social (and cultural) values, thereby accounting for a socio-cultural grounding of clinical research at its conceptual level. The plurality of meanings we discovered for these concepts points to an unfixed, indefinite, and impermanent character of the beliefs that are organized around them, including moral judgments. With these thoughts in mind, we now turn to an analysis of ethical reflection regarding clinical research.
CHAPTER 3

ETHICAL REFLECTIONS ON CLINICAL RESEARCH

The need for an ethics of clinical research

Ethical issues of biomedicine and health policy have been given considerable attention in the second half of the twentieth century and the turn of the twenty-first, especially because the development of new medical technologies seem—as we have seen in the previous chapters—to be revolutionizing the face and future of medicine, and challenging our traditional understandings of human life. Moreover, clinical research, as a complex, hybrid medical enterprise, where medicine-as-care meets medicine-as-science, constitutes a social environment with ambiguous roles to be played by the centrally involved parties; that is, the researchers and research subjects. This is so because the physician-patient relationship, which is roughly understood in terms of what the physician can do for the patient, is frustrated under research conditions, whereby much of the experimental endeavor points to what the patient-subject can do for the physician-researcher.

As explained at the beginning of the thesis, the mission of clinical research is to produce fresh insight into the biology of disease, and thus respond to human health necessities by contributing to the generation of life-saving/enhancing therapies. It is basically the capacity to improve individual and public health that defines the social significance of clinical research (if not of modern medicine itself), and offers the grounds for its ethical justification. Yet, it seems that, in seeking validation of new therapies, modern medicine faces an impossible dilemma: If it ventures into a rigorous testing of new therapies in the context of research, especially for conditions for which no other proven therapy exists, it will be accused of exploiting diseased
bodies, and persons, to gain knowledge. If it attempts to apply unproven therapies to patients in the context of health care, it will be accused of taking risks with people’s health.169

However, the need for new safe and effective therapies is as real as ever, and points to the processes of clinical research as they have been described. This necessity requires the development of morally justified rules to see these processes through and, by extension, it calls for a normative theory to place the conceptual and technical features of clinical research in some kind of moral perspective. The ethical theorizing (and evaluation) of clinical research is part of the broader philosophical project of providing the conceptual tools needed for analyzing and understanding emerging practical issues (in research, in this case) in a systematic way. Without this language of abstraction, we would be unable to view and comprehend phenomena and empirical facts of clinical research, let alone assess them in relevant ethical terms.170

The emergence of bioethics and its intellectual significance

The intellectual task of providing these conceptual tools—that is, systematic theories and methods—is the discipline of modern bioethics, otherwise known as medical or biomedical ethics (all terms being used interchangeably). Although historically rooted in the legacy of Nuremberg, bioethics began its development in the early 1960s, and took off, as an intellectual pursuit, in the 1970s.171 Its development is seen as the response to medical issues of serious ethical concern that, at the time, raised debates not only within the medical profession, but also—and for the first time—in the public space. One such debate concerned the ethics of “triage” (a method of micro-allocation of treatment by patient-exclusion according to specific criteria) in

169 Baum I

170 “…philosophical theorizing has practical political value…. [that] lies in its abstract and systematic character.” Nussbaum 10

171 Wolpe 39
making blood dialysis available.\textsuperscript{172} The other debate was related to the exposure of serious medical misconduct, recognized as deception and coercion of vulnerable subjects, in the context of human experimentation.\textsuperscript{173}

Therefore, the issues that prompted these debates, and the subsequent development of bioethics, were related to patients’ access to limited health care resources and the treatment of human subjects in clinical research. But the emerging idea behind these developments, and one that gradually obtained more and more currency, was the understanding that the patient is a moral agent with an independent voice in the medical decision-making process. This new idea challenged the traditional ethics and practices of the medical profession, whose paternalistic posture had only recognized the physician as the sole broker of a patient’s health and health-related decisions.\textsuperscript{174}

The fact that these debates became public meant that, for the first time, ethical reflection on medical issues was engaged in by non-physicians, and what was once the exclusive discourse of medical ethics, internal to the medical profession, was now penetrated by philosophers and theologians (some Catholic, but mostly Protestant). In seeking to address issues of justice in health-care allocation and the physician-patient relationship (as we have just seen), these scholars and moral thinkers established the intellectual space of \textit{bioethics}. This body of work

\textsuperscript{172} Emerging in the early 1960s, this technology held vast therapeutic promise for overwhelming numbers of patients, when comparatively few such facilities existed. Ibid

\textsuperscript{173} Such misconduct was exposed by Hornblum’s truncheon studies of the skin experiments in Holmesburg Prison, Philadelphia. Henry Beecher’s 1966 article on clinical research detailed 22 examples of deceptive experiments conducted from 1948 to 1965 without subject consent. Hornblum; Beecher

\textsuperscript{174} Wolpe 39
was soon institutionalized, and has since spread, as a distinct field, across various academic programs within (mainly) philosophy departments, and numerous publications, around the country.

The goals of this chapter

In this last chapter, I shall explore what bioethics has to offer currently in terms of the major bioethical theory, which is used to guide the processes of modern medicine and clinical research. I will then explicate a set of HIV/AIDS clinical trials, conducted in various developing nations, which investigated the efficacy of a therapy to prevent the mother-to-infant transmission of HIV. These trials are used here as a case study to show how such research is conducted in the field, and how it is ethically evaluated within the normative context of the dominant bioethical theory.

However, I argue that the bioethical approach in question has limited normative power, as it is geared toward a narrow, procedural evaluation of research ethics. Therefore, the exclusive application of bioethics (or, at least, this dominant bioethics) does not suffice to achieve a deeper moral understanding of transnational trials, and particularly with respect to their claims of justice. The ethical dimension of clinical research, as a social institution of international scope, must also be analyzed in the context of the social, economic, and political circumstances of developing nations, within which international trials are mainly hosted.

In doing so, we need to acknowledge the pervasive use of clinical trials as a substitute for health care for the thousands of subjects involved in them. This realization should raise

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The Hastings Center (1969), and the Kennedy Institute at Georgetown University (1971) were the first ones to be founded. Wolpe 39
skepticism about the ethical merits of clinical research conducted in the Third world, simply because the choice between health care and clinical research—especially for HIV-positive patients—is not a real option, as health care resources are extremely scarce.

Moreover, the explication of the conceptual basis of clinical research conducted in the second chapter of the thesis points to an ethics of research (indeed, of biomedicine in general) rooted in unfixed conceptualizations of health, disease, and human wellbeing and body. As these notions are mostly socially and culturally shaped, the ethical thought that emerges from them (as an ontological basis) is similarly unstable, and contingent on social and cultural values, in spite of any universal power that may be ascribed to its normative claims. It is, therefore, possible to argue that an emphasis on a different set of social values (i.e. a specific notion of human flourishing, the right of all people to such flourishing, etc.) can generate an alternative ethical and normative framework for clinical research assessment, especially at the transnational level.

Indeed, this thesis will be concluded with the brief exploration of a framework of normative principles, whose conceptual basis is an intuitive notion of human dignity. This concept brings about values of distributive social justice grounded in the idea that each and every person is entitled to material opportunities that can afford them the flourishing of their human capabilities. This idea has particular strength when it concerns the weakest members of society, such as women and children, as the framework proposes the constitutional adoption of its normative principles as minimal political goods.

As a partial theory of justice, this framework does not speak directly to ethical issues of clinical research, but nonetheless raises some important questions as to what constitutes an

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176 Bioethical inquiry is being increasingly penetrated by other disciplines, such as history, social science, or anthropology, thereby taking new directions, other than philosophical ones (i.e. medical anthropology).
appropriate socio-economic and political environment that may render transnational clinical research more ethical. For instance, the right to adequate health care and nutrition, protected constitutionally by some national governments and afforded to all of their citizens, means that HIV-infected patients will not resort to clinical research to obtain basic care, nor will clinical trials be designed to exploit the vulnerability of resource-poor communities in an effort to recruit significant numbers of subjects.

In such a social context, clinical research can be the object of truly meaningful ethical evaluation, as it will not constitute a venture of badly needed health care, but an actual option for citizens to participate in a scientific endeavor with the potential to generate new, safe and effective therapies for their communities and the entire humanity. Although a full critique of the human capabilities approach is beyond the scope of my thesis, it is my aim to (at least) introduce it as a more complicated biopolitical, conceptual and normative, context, in which a more radical ethical analysis of (transnational) clinical research can be achieved. It is only in this context, I argue, that a subsequent bioethical analysis of research procedures seems fair and meaningful.

The principlist bioethical model: philosophical roots and implications

Let us then visit immediately the most important bioethical theory, as formulated by bioethicists Tom Beauchamp and James Childress. This, in fact, is not a complete moral theory, but rather an analytical framework consisting of four general principles (also accepted by classical ethical theories, such as utilitarianism, virtue ethics, Kantian ethics, etc.) that help to reason through bioethical problems. It is a deductive (top-down) approach of an applied practical ethics, which means it is anchored in moving from the general to the specific; in other
words, from broad-spectrum norms to specific cases.177 The emphasis and reliance on principles has led to the name “principlism” as a characterization of this ethical methodology. As an instance of applied ethics, this principlist model offers the basis for guidelines to be used in professional (medical) ethics applied in both medical practice and clinical research.178

The validity of the four bioethical principles is claimed by its authors to be grounded in common morality, which includes rules whose underlying general values are expressed in these principles.179 “Common morality” is not a moral theory per se, but is defined as “the set of norms that all morally serious persons share…and [which] bind all persons in all places.”180 Therefore, the authors (and their bioethical theory) endorse a “universal core of morality” that is distinguished from, say, community-specific morality, which includes moral norms deriving from “particular cultural, religious, and institutional sources.”181 An important implication of the

177 “Justification occurs if and only if general principles and rules, together with the relevant facts of a situation, support an inference to the correct or justified judgment(s).” Beauchamp and Childress 385 (2001)

178 Although dominant, the deductive bioethical model has been rivaled by the so-called casuistic method advocating a case-by-case evaluation. This is a bottom-up approach of Aristotelian origin that accepts the primacy of practical decision-making based on precedent and common moral judgments. Casuists maintain—rightly, I think—that the very matrix of general principles and rules (i.e. the conceptual framework of the deductive model) is created out of moral judgments that can only be made through an initial stage of moral reasoning over the specific, and not the general; that is, through induction, and not deduction. General moral rules can be fully understood only in terms of the paradigmatic cases which define their meaning. For an explication of the precepts and limits of casuistry, see Beauchamp and Childress 391-397 (2001); for a defense of casuistry, see Toulmin; for a criticism of casuistry, see Arras 175-183.

179 Beauchamp and Childress 11 (2001)

180 Ibid. 3

181 Ibid.
accepted universality of common morality is that the bioethical principles are (in theory, at least) applicable in clinical research conducted anywhere in the world.\footnote{182}

Moreover, there is a degree of indeterminacy built in this model, in the sense that the principles are very general and abstract, so as to avoid determining moral judgments, or the kinds of acts that should be performed, based on the principles alone, or solely on the rules they generate. This is so because principles (and rules) have no sufficient content that may lead to specific moral judgments and courses of action. Instead, they have to derive their content from beliefs about facts, cultural expectations, precedents, and the like that form the specific contexts (social, cultural, political, etc.) of cases and policies in biomedicine.\footnote{183} Therefore, principles (and respective rules) have to be contextualized, or specified, and their relative weights and strengths must be balanced when their added contents happen to be antagonistic.\footnote{184}

For instance, respecting people’s wishes in therapy (according to the principle of respect for autonomy) may conflict with the norm of avoiding producing harm (principle of nonmaleficence). This would be the case of a Jehovah’s witness refusing blood transfusion for his child. The two principles must be specified in terms of all available details (medical, factual, cultural, religious, etc.), and then balanced in a way that one of them may prevail in determining the course of action to be taken in resolving this ethical dilemma. These processes of specification and balancing of principles are necessary if principles and rules are to be applicable

\footnote{182}{In the first chapter, extensive reference was made to competing analytical approaches to ethical reflection of the basis of universalist and relativist views. Ch. 1 22-6}

\footnote{183}{Beauchamp and Childress 15-6 (2001)}

\footnote{184}{Ibid. 17-8}
in resolving practical problems in bioethics, both in medical practice and research, as well as in producing policy.¹⁸⁵

The principle of respect for autonomy

Let us now move to the principles themselves and their explication. The bioethical model I am considering consists of the following general norms: 1) respect for autonomy, 2) nonmaleficence, 3) beneficence, and 4) justice. First, Respect for autonomy is a principle based on moral and political conceptualizations of individual freedom and choice rooted in the liberal tradition.¹⁸⁶ In its basic form, the principle points to “respecting the decision-making capacities of autonomous persons.”¹¹⁸⁷ The central concept here is, obviously, autonomy whose meaning with respect to the individual includes two basic conditions: freedom from external influence and control (liberty), and the capacity for voluntary and intentional action (agency).¹⁸⁸

An important bioethical concern connected with patient or subject autonomy has to do with inadequate levels of understanding that may prevent a person from making a meaningful informed decision. This may be due to external constraint (e.g. deliberate withholding of crucial pertinent information as happened in, say, the Tuskegee study), or mental incapacitation.¹⁸⁹ In either case, individual autonomy is diminished, but it is the first case that manifests a patronizing

¹⁸⁵ Ibid.
¹⁸⁶ Beauchamp and Walters 19
¹⁸⁷ Ibid. 12
¹⁸⁸ Beauchamp and Childress 58 (2001)
¹⁸⁹ Diminished autonomy because of mental disability recognizes the right of the individual to have an appropriate autonomous proxy acting on his/her behalf, and for a person’s best interests, or some other form of surrogate decision-making. For a discussion on the protection of incompetent patients. Ibid. 152-7
and/or coercive approach toward the individual, and becomes the target of criticism in light of this principle.

An important part of the content of autonomy is the individual’s possibility to make choices reflecting his/her personal values (which may be religious/metaphysical, secular, and the like), beliefs and perspectives (which may well be socially- and culturally-constructed), and the right to do so. Respect for autonomy thus requires recognizing and honoring this right, and the entitlement of persons to determine their own destiny (to the extent that they do). Therefore, two basic rules deriving from this principle are truth telling on the part of the physician or researcher, and obtaining voluntary and informed consent from a patient or research subject about the kinds of medical interventions one has agreed on in his/her case.

In this regard, the respect-for-autonomy norm is consistent with the Kantian understanding of persons having intrinsic value, and not value conferred upon them by special circumstances. Lastly, respect for autonomy must be specified in the context in which it is to be applied, and balanced against other principles. In this process, respect for autonomy may even be restricted if it conflicts with other accepted values, such as that of justice concerning the distribution of scarce health care resources.

The principle of nonmaleficence

Second, the principle of nonmaleficence refers to an obligation not to inflict harm on others, and is associated with the classical dictum primum non nocere, or “first, do no harm.”

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190 In other words, this principle recognizes that persons must be treated as ends in themselves, and not as mere instruments serving given ends. Beauchamp and Walters 19

191 Ibid. 20

192 Beauchamp and Childress 113 (2001)
Nonmaleficence has been typically conflated, into a single principle, with beneficence, which refers to “acts involving prevention of harm, removal of harmful conditions, and positive benefiting,”193 or “the duty to confer benefits and actively to prevent and remove harms…in biomedical and behavioral contexts.”194 However, because of important distinctions between the two principles, and ways in which they are interpreted in multiple biomedical contexts, nonmaleficence is considered a separate norm in the current principlist bioethical model. Indeed, in a narrower sense, the obligation to avoid causing harm to others does not entail an obligation to help them.195

The concept of harm that is relevant to this principle is construed as “thwarting, defeating, or setting back some party’s interests,”196 whether these actions may, or may not, be justifiably wrong. The emphasis here is on physical harms, such as pain, injury, death, and even mental harms and other setbacks. In particular, the principle of nonmaleficence refers to distinctions between “killing and letting die, intending and foreseeing harmful outcomes, withholding and withdrawing life-sustaining treatments, and extraordinary and ordinary treatments.”197 In the context of medical care, these distinctions have particular weight in the cases of the terminally ill or the severely injured.

193 Beauchamp and Childress 135 (1989)
194 Ibid. 136
195 Although the principle of nonmaleficence seems to be more stringent (as in the case of committing a moral wrong on someone by producing a great benefit for another) than that of beneficence, any one of the two principles may override the other under particular circumstances, which have to be considered according to rules of specification and balancing. Beauchamp and Childress 114-5 (2001)
196 Ibid. 116
197 Ibid. 113
The relevance of the principle is quite considerable in a clinical research environment, whereby distinctions between legitimate and undue research risk, or providing therapeutic benefit while conducting rigorous testing of the research hypothesis, are important considerations. These can be viewed in light of several technical features involved in research, such as trial randomization, the single or double blinding of a trial, the existence of genuine equipoise, the termination or completion of a trial, the involvement of a data-and-safety monitoring committee, the possibility of a subject to withdraw from a study, the process of voluntary and informed consent, and the use of placebo in a study’s control arm.

Issues related to these features are addressed as the rest of the principles, and especially that of justice, will be explained. However, it would be helpful at this point to briefly elucidate some of the most technical features that will become a substantial theme in the rest of the thesis. Thus, as was explained in the second chapter, trial randomization refers to the random assignment of subjects to groups receiving either the experimental treatment, or control treatment(s) including placebo. This technique was conceived as a means of enhancing the rigor of comparisons of the outcomes regarding drug efficacy or safety in each group of the study.\textsuperscript{198}

Another technique, intended as a means of enhancing scientific impartiality by avoiding the contamination of the results from human bias and preconceptions, is the single or double blinding of a trial. This method refers to a research design in which subjects and subjects/researchers respectively do not know which treatment (whether control or experimental) has been applied to which subject.\textsuperscript{199}

\textsuperscript{198} Ch. 2 73-4
\textsuperscript{199} Ibid. 76-7
Moreover, in the research context, equipoise refers to “a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial,” including the arm that may be assigned a placebo. In this sense, the researcher has (and should have) no treatment preference until the outcome(s) of a trial point(s) to the superiority (in safety/efficacy) of a specific treatment compared to the tested alternative one(s), whereby we say that equipoise has been “disturbed.”200

Theoretically, equipoise is an ethical condition of all cases of clinical research, including trials in which a treatment of already known safety/efficacy (as opposed to placebo) is applied in the control arm. This specific variant of equipoise, which strives to evaluate the safety/efficacy of an untested therapy against a best-proven one, leads to a type of research known as an equivalence study. In practice, “equivalence” signifies no use of placebo in a trial, whereas “equipoise” usually brings to mind a placebo-controlled study.201

Despite their scientific merits, the randomization and single/double blinding trial techniques are not without their medical risks and ethical challenges. The no-access policy to obtained data in a trial may lead, at times, to serious health setbacks of involved subjects, as (concealed) critical health information does not necessarily translate into immediately visible symptoms. To ensure subject protection from additional health risk, or simply (but importantly) to promptly recognize results that respond effectively to the study hypothesis, trials incorporate the structure of oversight (or monitoring) scientific committees, which have constant access to incoming data, and can interpret them statistically.202

200 Freedman 429

201 Ibid.

202 For a discussion of the role of monitoring committees, see Beauchamp and Childress 326 (2001)
Subjects have the right to withdraw from research that imperils their health, or the whole trial can be suddenly “terminated” (before the time of its anticipated completion) when equipoise is disturbed. In the latter case, the “unmasking” of interim results points to the demonstration, beyond reasonable doubt, of the superiority of a specific treatment (or the inferiority of another). Research ethics requires that all enrolled subjects be offered the superior drug, which then becomes the “standard of care.”

The principle of beneficence

Third, the principle of beneficence, in the usage of the principlist model, “establishes an obligation to help others and further their important and legitimate interests.” Therefore, beneficence requires taking positive steps to promote the welfare of others by, say, protecting and defending their rights, rescuing them from danger, or helping persons with disabilities. In therapeutic contexts, beneficence demands the welfare of patients as a goal of health care, and “the promotion of health by cure or prevention of disease.”

Although there seems to be no clear line we can draw in the continuum of providing benefit and not inflicting harm, the bioethical principlist model recognizes distinctions between the norms of nonmaleficence and beneficence. For instance, in light of a principle of utility, a

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203 There is a long standing debate as to what constitutes the “standard of care.” Certain authors argue in favor of a single standard worldwide once a particular therapy is (somewhere) identified as the “best-proven” one for a specific health condition. Others claim that the standard of care can consist of “less than the best methods” if they have “sufficient social value,” which is defined in terms of the importance of the health concern these lesser methods are designed to address, and the local circumstances (medical, social, economic, etc.) in which they at to be applied. Freedman 429; Wendler et al. 923-5

204 Beauchamp and Childress 166 (2001)

205 Ibid. 167

206 Beauchamp and Walters 20
version of the norm of beneficence entails that “agents balance benefits and drawbacks to produce the best overall results.” Therefore, although the principle of nonmaleficence seems more stringent, an obligation for beneficence can take precedence when a major benefit can be conferred by causing only minor harm, or when a great many people can be benefited through the minor harm of a few. This idea pertains especially to the goals and interests of clinical research, whereby the design of appropriate research guidelines is key to balancing benefits, risks, and costs in clinical research. This task can be seen partly as an effort to balance the principles of beneficence and nonmaleficence.

Conflicts between the principle of respect for autonomy and that of beneficence occur when patients’ freedom to make their own therapeutic choices is curtailed through the deliberate nonacquiescence, or intervention, of physicians, whose intentions are to benefit, or prevent harm to, their patients. This paternalistic conduct frequently involves what is assumed to be benevolent withholding of information from the patient, on the grounds that he/she is incapable, psychologically or mentally, of bearing the emotional weight of medical disclosures, and/or reflecting upon them to make a personal decision. Medical paternalism is embodied in numerous kinds of situations, so that detailed specification and careful balancing of the two principles (respect for autonomy and beneficence) is crucial in resolving related conflicts.

207 Beauchamp and Childress 165 (2001)

208 Ibid. 168

209 Paternalism is here defined as “the intentional overriding of one person’s known preferences or actions by another person, where the person who overrides justifies the action by the goal of benefiting or avoiding harm to the person whose preferences or actions are overridden.” Ibid. 178
In the context of clinical research, the principle of beneficence is meaningful in two senses, which nonetheless contain more conflicts: First, patient-subjects are usually expected to draw a more-or-less substantial benefit from their participation in research, especially when no other proven therapy exists to address their condition. Yet, no such benefit is conferred on subjects included in the placebo control arms of randomized controlled trials (RCTs), although these patients assume the same burdens and risks of research. This conflict may be resolved by balancing the principle of beneficence and that of respect for autonomy, provided that all the requirements regarding the consent process are meticulously adhered to, so that autonomy may be genuinely respected.

Second, the chief contribution of clinical research to the promotion of health (and, consequently, the benefit of society) comes from the generation of therapies for future patients. This melioristic goal of research involves present patients who may, or may not, receive a therapeutic benefit (as already explained), especially if included in a placebo randomized trial.210 This is a conflict between the norm of beneficence and the principle of justice, whose ramifications, and balancing with beneficence, will be explained immediately.

The principle of justice

Justice, the fourth and last principle of this bioethical model, is of central importance with regard to issues of health policy that are connected with the allocation of health care resources. The idea of justice may be defined as “fair, equitable, and appropriate treatment in light of what is due or owed to persons,”211 and points to a notion of distributive justice, which

\[\text{\footnotesize\textsuperscript{210}} \text{ For a detailed, and fascinating, discussion of the ethical implications of melioristic research for the benefit of society, see Jonas.} \]

\[\text{\footnotesize\textsuperscript{211}} \text{ Beauchamp and Childress 226 (2001)} \]
enables an analysis of social inequalities. Inequalities in accessing scarce health resources are due to the cost of health care and/or health insurance, and, in addressing them as a social problem, several disparate objectives must be reconciled: some sort of access to health care that may be considered fair, personal preference in selecting a health plan, a free-market economy, and health promotion across society.

The conceptual basis of the principle of justice is the notion of equality, which leads to a formal principle stipulating that equals should be treated equally, or like cases should be treated alike. From this norm, several material principles of justice emerge, specifying how like cases can be treated alike, or equal people equally, with regard to substantive criteria, such as individual need, acquisition in a free market, individual effort, societal contribution, and merit (among other things).

We have already presented brief accounts of egalitarian and libertarian views on distributive justice, and have seen how the egalitarian view would favor distribution of (limited) health care resources according to people’s individual health needs, which, in turn, determine people’s (physical and mental) possibilities to find social opportunities of happiness and flourishing. By contrast, the libertarian view supports distribution by appeal to people’s purchasing power in a free market environment, and this power is additionally supported by

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212 Ibid. 225.

213 Ibid.

214 Articulations such as “to each person according to need” or “to each person according to free-market exchanges” are some of these material principles of justice. Ibid. 228

215 Ch. 2 54-6
claims of freedom of choice. These, and other, theories claim to offer justifiable accounts of justice, yet they interpret it in diverse ways.  

The meaning of justice in clinical research: protection vs. access

Let us now examine the ramifications of the principle of justice for clinical research involving human subjects. Traditionally, the paradigm for ethical analysis regarding research justice had focused on concerns about how to fairly distribute the benefits, burdens, and risks of research among subjects (as individuals and as social groups), and how to protect them from harm and exploitation, especially in the context of non-therapeutic research. We have already mentioned instances of abusive research in the U.S., whereby “vulnerable” populations, such as racial minorities, the economically disadvantaged, the institutionalized, or the incarcerated, had been conveniently recruited, and typically exploited because of their special circumstances and lack of power.

Yet, as the protectionist paradigm of justice took hold in the 1970s, and eventually led to attitudes of overprotection of subjects (not to mention the public distrust toward research), vulnerable groups (which came to also include children, women, the very sick, and the mentally incapacitated) were increasingly excluded from trials. The result was an unfortunate lack of tested, safe and effective therapies that could be responsive to the specific health needs of these populations (and which, to some degree, still persists to date). Therefore, it became apparent that

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216 For a brief account of extant theories of justice, see Beauchamp and Childress 230-5 (2001).

217 The non-therapeutic skin experiments in Holmesburg Prison, Philadelphia, are a case in point. Ch. 1 17-8

218 For a brief history of abusive research, and resulting changes in research policy, see McCarthy.
concerns of subject protection had to be reconciled with a social need for research, while individual subjects could also be afforded some kind of benefit for participation in trials.

Moreover, the American historical experience with HIV/AIDS changed much of the public approach to research during the 1980s, and particularly that concerning thousands of infected individuals who struggled for some kind of effective treatment when AIDS research and therapy were greatly limited. As I have mentioned in the first chapter, advocacy groups for HIV-positive individuals pressed for increased participation in clinical trials, whereby experimental therapies were perceived as top-of-the-line treatments for individual patients. As people actively sought to be included in research and reap its benefits (perceived or real), a new paradigm for research justice emerged, which has focused on concerns of fairness in distributing the benefits of research. In other words, this new approach assumes that “participation in medical research is more of a benefit to be sought than a burden or risk” from which patient-subject would need protection.

Seeking inclusion in clinical trials as a way to access therapy is a somewhat ironic feature of research because of the uncertainty involved in trials with respect to their prospect of offering substantial therapeutic benefit to every participant. However, if the principle of justice must be interpreted and applied solely in the context of fair access to clinical research and its possible benefits, one has to define what this fairness (in access) exactly means. There are two perspectives from which one must examine this issue: the decision-making on how to select

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219 Beauchamp and Childress 226-7 (2001)

220 Powers 154

221 Beauchamp and Childress 227 (2001)

222 Powers 154
Justice in inclusive/exclusive research, and the question of present and future patients

The first class of considerations refers to decisions about which prospective subjects to include in a trial, and which to exclude. This is a delicate balancing act that requires finding ways to allow people’s fair and equitable access to research and its potential benefits, while ensuring that the selection of these subjects is appropriately responsive to the primary aim of research, which is to generate new knowledge. In other words, the inclusion of specific subjects (and the exclusion of others) must satisfy certain medical and scientific criteria, according to which data collected from subjects in the course of a study may be meaningful in answering the research hypothesis.

It is, therefore, up to the investigators to specify what sort of health status would contribute positively to the statistical power of the results of the study, and what would instead compromise it. This would mean that assessing people’s condition of health before the onset of a study is extremely significant for their prospects of inclusion or exclusion. The issue becomes even more complicated and challenging in the case of specific diseases involving substantial suffering and death, such as certain types of cancer, for which no successful therapies exist. In the context of such diseases, patients tend to view research of new treatments as health care to which they should be entitled. Therefore, the ethical challenge of serving justice, viewed as fair access to clinical research, becomes uncomfortably blurred as it, more and more, resembles justice in allocating (scarce) health care resources.

On the other hand, a serious concern of justice in fairly distributing research benefits should pose the question “benefit for whom?” As I have pointed out, research is (conceptually,
at least) a project that intends to produce biological answers to biological questions with the ultimate goal of generating new safe and effective therapies. In this sense, the real beneficiaries of research are not present, but future, patients who will reap the full benefit of other people’s investment in it (i.e. bearing its risks and burdens).

At the same time, one should never lose sight of the relatively recent history of research abuse, as such exploitation is easily repeated. The issue of subject protection is by no means (and should never be) a thing of the past. In view of the ease of sacrificing present patients on the altar of future human wellbeing, the least the institution of clinical research (and, by extension, of society) can do is provide adequate protection to those human beings who undertake the burdens of improving our future lot in the area of health.

Therefore, how should research be structured to balance concerns about fair inclusion of subjects (both at the individual and societal level), a benefit for both present and future patients, protection from undue risk and harm, and rigorous (yet, ethical) testing of therapies to satisfy the scientific requirements of the research project in medicine? Research policy makers have attempted various responses to this question.

For one thing, researchers should take special care in determining the acceptable level of risk in clinical trials, so that trials may become more inclusive of vulnerable groups without jeopardizing subjects’ health. It should be remembered that justice-as-protection does not mean exclusion, especially when research is needed to respond to health issues of specific populations. Therefore, the consent procedure should be appropriately designed, and thoroughly respected (i.e. with the proper disclosures and explanations), in order to secure people’s genuinely autonomous decisions regarding trial participation.
On the other hand, it is uncertain whether justice in research can be successfully construed in terms of accessing benefits. “The real issue of justice…is not the right of subjects to be subjects.” It is rather, I think, affording some benefit to all subjects, notwithstanding the fact that control subjects may, or may not, receive an active drug. As therapeutic benefit is not a reasonable expectation in many cases, special care must be given to at least minimizing the risk of research. For this reason, decisions about conducting equipoise studies employing placebo in the control arms must be rigorously justified. Moreover, research protocols typically offer some form of compensation (e.g. monetary) for research participants, so that they all obtain some kind of benefit, with the provision that compensation be minimal enough, yet fair, to prevent undue inducement for participation.

Finally, apart from these procedural forms of ensuring justice, the issue has received special consideration with regard to transnational research conducted in developing nations, whose economies cannot support expensive treatments. In this case, other less costly treatments can be tested in these nations, with the provision that they can be afforded by the governments in those countries and be made reasonably available to their societies once they are fully developed. It is also an ethical imperative, and a formal condition, for research (whether

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223 Ibid. 157

224 As mentioned in the explanation of placebo-controlled equipoise studies, when no proven therapy exists to be applied as a control treatment, subjects in the control group receive no real drug; hence, no therapeutic benefit.

225 CIOMS guideline 7 states that “the payments should not be so large, however, or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better judgment (‘undue inducement’).” The Council for International Organizations of Medical Sciences (CIOMS - 2002)

226 CIOMS guideline 10 states that “before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure
conducted in resource-poor countries or on subjects from vulnerable groups) that it should respond to the health needs of the populations from which subjects are recruited for trials.\textsuperscript{227} In this way, whatever benefit research can provide will certainly be conferred on people who need it.

The ACTG 076 transnational clinical studies

After the exploration of the principlist bioethical framework and its implications for clinical research, I shall now turn to a discussion of a set of HIV/AIDS trials, sponsored by Western funding and research organizations, that involved subject-patients in the developing world. This research is presented as a case study of how the dominant, four-principle bioethical model we have analyzed can be applied (as it actually was) in the context of international clinical research. These trials are also explored as a significant instance of ethical contestation of clinical research, with regard to moral standards of beneficence and justice.

However, my major intention in using these trials as a case study is to illustrate features of research that underscore the complexities in the meaning of research justice. It is also my aim to show that striving to achieve justice in clinical research goes beyond the procedural approach that focuses on fair access to research benefits (which constitutes the current paradigmatic meaning of research justice in principlist bioethics). Questions of justice in clinical trials cannot be properly separated from issues of distributive justice in health care, precisely because (as we have frequently seen so far) the “benefits” of research are sought after as therapeutic benefits equaling (or even surpassing) those of available health care. This is true in both developing and

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\textsuperscript{227} CIOMS guideline 10 also states that “the research [must be] responsive to the health needs and the priorities of the population or community in which it is to be carried out.” Ibid.
industrialized nations, but more so in the former case, whereby people have little choice other than enrolling in research as their only means to obtain care.

The trials we will examine occurred in the early 1990s, when the AIDS epidemic was already rampant in various places of the world, but had shown its greatest ferocity in sub-Saharan Africa, the most severely HIV-afflicted area worldwide. To this day, millions of infected victims have perished, leaving behind more millions of orphans and other dependents. In a region where the proportion of adolescents and adults (15 to 49 years old) living with HIV is 8.8%, AIDS has attained the levels of a pandemic devastating the younger and most productive segments of society. In the HIV-infected population, women comprise 55%, a far too perilous score considering that the “natural” rate of the perinatal (mother-to-infant) transmission of HIV is 25%.

The struggle against HIV and AIDS has been waged on several fronts such as prevention, education of the public, antiretroviral therapies, and clinical research for the development of such antiretrovirals and vaccines. Yet, while transmission rates of HIV have been substantially reduced in the Western world thanks to the development and availability of retroviral drugs, developing nations have been facing an almost vertical increase in transmission rates, mainly due to the lack of the same therapies that have so tremendously benefited the West.

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228 UNAIDS

229 Ibid.

230 This figure is corroborated by Lurie and Wolfe, stating that the perinatal HIV transmission in placebo groups of ACTG 076 trials (that is, the transmission rate in subjects who receive no active preventive treatment) is 25%. Grady 35-36; Lurie and Wolfe 855

231 Antiretroviral drugs refer to the structure of HIV, which is a “retrovirus,” meaning that its nucleic material is RNA, and not DNA.
The story of clinical research that will interest us here starts in 1994 at the conclusion of studies conducted in the United States that had tested, for the first time, the efficacy of an AZT-based regimen in preventing the perinatal transmission of HIV. Designated as ACTG 076, these placebo-controlled equipoise trials were interrupted (and rightly so) as soon as equipoise was disturbed; that is, upon demonstration of the efficacy of the experimental treatment (against a placebo). Indeed, the application of the so-called ACTG 076 regimen had been shown to reduce the rate of HIV infection in newborns by two thirds; that is, from 25% to 8%.

The ACTG regimen was promptly recommended as the best-proven therapy for perinatal HIV transmission, and as the “standard of care” in North America and Europe, thereby becoming available to the majority of pregnant HIV-positive women in the West. However, its cost of over $800 per mother and infant was prohibitive for women in the developing world, and particularly those in sub-Saharan Africa, where the annual per capita health care allowance was between $5 and $10 (excepting Zimbabwe; $86). If the perinatal HIV transmission were to be controlled in the worst AIDS-afflicted (and poorest) areas of the world, an affordable regimen

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232 AZT (short for “Zidovudine,” developed by GlaxoWellcome) has been the quintessential drug in treating early, advanced, or no apparent symptoms of HIV infection, and shown to slow down viral reproduction and the destruction of the human immune system.

233 This designation stands for AIDS Clinical Trials Group (study) 076. Luna 257

234 This figure is also corroborated by Lurie and Wolfe who mention an approximate 10% transmission rate in the experimental therapy groups of the trials. Grady 35-36; Lurie and Wolfe 855

235 However, “despite the proven benefits, the [ACTG] 076 regimen is not universally used even in the United States. Some women are outside the health care system and fail to obtain optimal prenatal care.” Levine, C. 44 (1998)

236 According to other authors (Msamanga and Fawzi), “the average annual per capita expenditure on health is $11 for the region, and in several countries it is less than $4.” Msamanga and Fawzi 849; Annas and Grodin 561
had to be made available to pregnant, HIV-positive women there, and one that could be practically applied in a Third world setting. That meant that such a therapy had yet to be tested.

The decision to provide such a regimen to developing nations, and to test it on more than seventeen thousand women in various transnational sites, was taken at a World Health Association (WHO) meeting the same year.\(^{237}\) Thus, a series of eighteen randomized trials were designed, most of which would test the efficacy of a much shorter course of the standard ACTG 076 regimen as a preventive treatment.\(^{238}\) It is notable that three of the trials involved no placebo (the control groups would receive the standard ACTG 076), of which two were to be conducted in the United States and one in Thailand. The remaining fifteen placebo-controlled studies would be conducted in various sites in sub-Saharan Africa\(^ {239}\) and one in the Dominican Republic, while research protocols were approved by local IRBs in the host countries. Nine of the studies were funded by the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH), one by the UNAIDS Program, and the rest by foreign governments.\(^ {240}\)

The justification of the decision to test sub-standard therapies (the standard of therapy being the ACTG 076 which, as mentioned, had been tested in the U.S.) was based on two arguments: First, the studies were thought to respond to the health needs of Third world populations in light of the AIDS epidemic, which is the major health threat in these regions, and

\(^{237}\) Lurie and Wolfe 853

\(^{238}\) Some of the trials would test other simple and inexpensive interventions, such as a vitamin A-based therapy, intrapartum vaginal washings, and a form of immunotherapy. Ibid.

\(^{239}\) Ivory Coast, Uganda, Tanzania, South Africa, Malawi, Ethiopia, Burkina Faso, Zimbabwe, and Kenya. Ibid. 854

\(^{240}\) Ibid. 854
is largely due to perinatal HIV transmission. Secondly, the studies were also claimed to address the more specific economic priorities of Third world nations, whose primary requirement was to make treatments affordable to their citizens. Therefore, testing candidate therapies that these governments could possibly purchase (providing they proved safe and effective) was affirmed as both imperative and ethical.

While the trials were well under way, and data were being collected in the various research sites, a controversy about the ethical merits of the trials erupted in 1997, and brought several compelling questions to the fore. The challengers were Ralph Nader’s Public Citizen organization, in conjunction with Global Lawyers and Physicians (GLP), a group working for the worldwide promotion and protection of health-related provisions of the Universal Declaration of Human Rights. On the other side of the controversy were the research investigators (i.e. researchers and the pharmaceutical firm GlaxoWellcome), their funding agencies, and Third world officials (local IRBs) who had authorized the trials. The major criticism of the studies held that the design of placebo-controlled equipoise research was

241 In a paper about the effects of tuberculosis on HIV preventive therapies in sub-Saharan Africa, Msamanga and Fawzi mention that “with the increasing privatization of the health care sector, many health services…are available—but at a price…In fact, over 50 percent of the adult patients admitted to the hospital in Africa are infected with HIV, and many of them are unable to pay for care.” Msamanga and Fawzi 849

242 These arguments were claimed to be in accordance with CIOMS guideline 8 (note that this guideline was formulated in 1993, and is not part of the revised 2002 version) stating that “research involving subjects in underdeveloped communities…[must be] responsive to the health needs and the priorities of the community in which it is to be carried out.” One way to interpret the “priorities of the community” was to assume that these were mainly economic. The Council for International Organizations of Medical Sciences (CIOMS - 1993)

243 Peter Lurie and Sidney Wolfe were members of Public Citizen’s Health Research Group, and the physicians who brought attention to the studies.

244 Annas and Grodin 560
unjustified in view of an extant best-proven therapy, the standard (longer) ACTG 076, which could have been used in the control arms instead of placebo, and thereby help prevent hundreds of new unnecessary infections.\textsuperscript{245} The major point of contestation was, therefore, the question about the equipoise-vs.-equivalence design of the studies.

**Critique and defense of the ACTG 076 transnational studies**

Drs. Varmus and Satcher, spokespersons of NIH and CDC respectively, defended this research on various grounds. First, they explained the decision not to test the standard ACTG 076 regimen in countries of the Third world through an appeal to the principles of beneficence and justice. Specifically, they stated that testing a therapy (other than the standard ACTG 076) that is likely to respond to the health needs of the population participating in this research, “even if there were some risks associated with intervention,” was ethical because such a trial would be compatible with the norm of beneficence.\textsuperscript{246} In addition, they claimed that researchers “might not elect to support a trial of an intervention that was beyond the reach of the citizens of [resource-poor counties]…because that trial would not pass the test of justice.”\textsuperscript{247}

To buttress this argument, Varmus and Satcher explained that the application of the standard ACTG 076 regimen was not compatible with the particularities of Third world social conditions and cultural practices for various reasons. First, women would have to undergo HIV testing early in their pregnancy, and receive appropriate counseling to comply with a lengthy oral

\textsuperscript{245} In the view of Lurie and Wolfe, “most of these trials…[would] lead to hundreds of preventable HIV infections in infants.” Lurie and Wolfe 853

\textsuperscript{246} Varmus and Satcher 1004

\textsuperscript{247} Ibid.
regimen, and with the intravenous administration of the treatment.\textsuperscript{248} They would also have to refrain from breast-feeding, as HIV is known to be transmitted via mother’s milk.\textsuperscript{249} In addition, both mothers and infants would have to be carefully monitored for adverse effects of zidovudine.\textsuperscript{250}

According to Varmus and Satcher, none of these conditions for the safe testing of the standard ACTG 076 regimen could be met in sub-Saharan Africa, with the additional hurdle of the unknown safety of the drug in view of rampant anemia, malnutrition, and endemic diseases such as malaria and, most importantly, tuberculosis.\textsuperscript{251} They also stated that this regimen could not be exported in these countries, in any case, because of its prohibitive cost of more than $800 per mother and infant.\textsuperscript{252} Indeed, the argument about the economic infeasibility of the standard ACTG 076 in sub-Saharan Africa was one of the strongest claims they made in support of the studies.

However, the main ethical issue raised by the critics had nothing to do with the testing of the standard ACTG 076, but with the use of placebo in testing the shorter course\textsuperscript{253} of the regimen (or other sub-standard therapies). Indeed, Lurie and Wolfe made clear that among the

\begin{itemize}
\item \textsuperscript{248} The application of the standard ACTG 076 regimen required five daily oral administrations of AZT to women for the last two trimesters of pregnancy, intravenous AZT infusion during labor, and oral administration of AZT syrup to infants for the first five weeks of their lives. Luna 257
\item \textsuperscript{249} Varmus and Satcher 1004
\item \textsuperscript{250} Ibid.
\item \textsuperscript{251} For an account of the effects of rampant tuberculosis, making HIV preventive therapy very difficult to implement in sub-Saharan Africa, see Msamanga and Fawzi.
\item \textsuperscript{252} Varmus and Satcher 1004
\item \textsuperscript{253} This course would entail AZT administration to women for the last three to four months of pregnancy and a single postpartum dispensation of AZT syrup to infants.
\end{itemize}
“numerous areas of agreement between those conducting or defending these…studies…and those opposing [them]” was the realization that “identifying less expensive, similarly effective interventions [as the standard ACTG 076)] would be of enormous benefit, given the limited resources for medical care in most developing countries.”

Hence, by shifting the discussion to a completely different issue in the very first argument they raised in support of the studies, Varmus and Satcher attempted to destabilize the attack of their critics.

Yet, their arguments might have explained why the standard regimen could not be employed as a control in equipoise-designed studies, and thereby justify the use of placebo in the control arms. Instead, Varmus and Satcher defended the use of placebo on scientific grounds, at least in their own interpretation. Specifically, they stated that the only truly rigorous method to evaluate the HIV perinatal prevention (and safety) rates of the tested therapies was to respond directly to the question of whether interventions were better than nothing (i.e. placebo). This approach, they argued, “usually provides a faster answer with fewer subjects, but the same result might be achieved with more sites or more aggressive enrollment.”

An approach based on limiting the number of research subjects might be interpreted as reflecting concern about minimizing the potential research risk, at least in terms of the spread of new HIV infections that would occur during trials. Likewise, faster obtained answers to important research questions might be seen as enhancing the prospect of making the experimental therapies—if proven safe and effective—available to the larger society sooner. However, it is more likely that Varmus and Satcher favored placebo-controlled trials for their cost-effective testing procedures, and for supplying “definitive” information about the safety and

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254 Lurie and Wolfe 854
255 Varmus and Satcher 1004
efficacy of the experimental interventions. In this way, they argued, host governments would be provided with better knowledge about the cost-effectiveness of these treatments, in the places where they were tested, in order to make educated purchasing decisions.256

In their riposte to these arguments, Lurie and Wolfe presented statistical reasons in favor of equivalence studies that would employ the standard ACTG 076 regimen as a control treatment, and showed that only a slight increase in the numbers of subjects would be required for such alternative studies.257 They also argued that “on the basis of the [standard] ACTG 076 data [collected in the previous, U.S. trials], knowledge about the timing of perinatal transmission, and pharmacokinetic data, the researchers should have had every reason to believe that well-designed shorter regimens would be more effective than placebo.”258 Therefore, asking whether a shorter AZT course is better than nothing (placebo) was the “wrong research question.”259

Moreover, in opposing these equipoise studies, Marcia Angell, the editor of The New England Journal of Medicine where much of the controversy was voiced, argued that researchers’ “strong temptation to subordinate the subjects’ welfare to the objectives of the study”260 lacked ethical merit in the sense that their subjects’ wellbeing should be their primary

256 Ibid.

257 The estimated number for an equivalence study was 620 subjects, whereas a placebo-controlled one would require 500. Lurie and Wolfe 856

258 Ibid 854

259 Seven years later (2004), Wendler and co-authors made exactly the opposite argument on the basis of data collected in 1999-2000 during shorter-course AZT trials conducted in the U.S. and in some of the same developing countries. In their view, the new data showed that it had not been clear, “at the outset,” whether a shorter AZT course was actually effective, even to some extent. Thus, the requirement of assessing shorter AZT regimens against placebo seemed compelling and justified. Wendler et al. 924

260 Angell 847
responsibility, as required by the Declaration of Helsinki, the fundamental ethical code guiding human experimentation. Therefore, using an ethical argument, Angell attacked Varmus and Satcher’s contention that placebo equivalence studies provided the only scientifically compelling basis for assessing the efficacy of a shorter ACTG 076 regimen.

Angell’s argument hinged on the meaning of the “standard of care,” an issue of significant implications for transnational clinical trials, which are typically conducted in an environment of vastly unequal health care resources in comparison with those in sponsoring countries. Thus, the research risk that is due to placebo controls, and which lurks in the investigators’ (scientific) objective to obtain “a rapid, unambiguous answer to the research question,” was presented by the studies’ defenders as ethically justified on the grounds that it was no greater than the “risk beyond that associated with standard practice.”

As we have seen, in resource-poor countries the local “standard practice” is to provide no prophylaxis to the affected population, and this practice then defines the “standard of care” locally. Therefore, if the local standard amounts to “nothing,” using placebo (an inactive drug) as a control treatment in clinical studies conducted in these countries may be seen as justified. Indeed, according to various defenders of these studies, subjects in the placebo groups were no worse off than they would be outside the research context.

261 According to the fifth basic principle of the Declaration, “concern for the interests of the subject must always prevail over the interests of science and society,” while the sixth one states that “every precaution should be taken to…minimize the impact of the study on the subject’s physical and mental integrity.” World Medical Association 434-5

262 203n

263 Angell 847

264 Varmus and Satcher 1004
In contrast, a placebo equipoise study would be unethical and prohibited in a Western country where the application of a superior therapy is already the standard practice—longer ACTG 076 in this case. Critics thus argued that, under the circumstances, patients-subjects in developing countries may be easily used as convenient means to researchers’ ends, unless ethical safeguards are instituted in the form of accepting a single standard of care worldwide. Yet, the standard of care presents a highly controversial issue even to this day, and whether it should be locally or universally defined is still being debated.

As already mentioned, the defenders of the studies presented their placebo-based design as the only rigorous method for supplying host governments with the information they needed to make purchasing decisions later. Yet, critics of the studies interrogated this view in terms of research justice. Specifically, they raised the issue of the possibility to make the experimental therapy available to the affected populations who provided the research subjects (if it proved safe and effective). “When the researchable problem exists solely because of economic reasons, the research hypothesis must contain an economic component,” they argued.265 If hosts and sponsors of the studies could not, at the outset, show visible resources of funds that would permit the procurement of the tested therapy in the future, it was unethical to commence the studies in the first place.

Other ethical considerations in the context of these ACTG 076 transnational studies focused on the process of voluntary and informed consent that was followed in the recruitment of subjects, and whose importance is regarded paramount, both as reflecting respect for autonomy and in protecting subjects from harmful research. As already mentioned, the aim of an appropriate consent process is to preclude coercion or deception of prospective subjects, so that

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265 Glantz et al. 40
one may freely choose to participate in a trial. Researchers are thus obligated to provide subjects
with adequate and clear information about their status of health, the benefits, burdens, and risks
they may incur from participating in a specific study, and assurance of their right to withdraw at
any time during the trial.266

However, reports of extremely inadequate consent processes in the context of these
studies triggered more criticism of the trials. Certain women were apparently misinformed about
the use of placebo (not a concept they were familiar with), and were made to perceive the study
as health care, and not an experimental venue. Others were given less than five minutes to make
an enrollment decision after being informed about their HIV status for the first time. Still others
were not solicited for consent, whereas permission for their participation in research was asked,
on their account, from the male tribal or family elders,267 presumably in accordance with local
values and custom.268

In view of the flexibility with which guidelines of clinical research involving human
subjects, anywhere in the world, are interpreted to accommodate local norms and institutions
(not to speak of the investigators’ research objectives), one may ask whether cultural and ethical
differences between developed and developing nations can be reconciled; indeed, whether ethical
collaborative research is possible. Critics of the studies argued that no Western sponsorship of
research is justified unless the same high ethical standards are adhered to in every setting of
international research. The relaxation of stringent, yet important, rules of research, on the

266 Gert et al. 151-2

267 Levine, C. 45 (1998)

268 Because no relevant information is available, it is hard to know to what extent obtaining
consent from male elders was a product of the ease it produced for the investigators, and to what
extent the women themselves adhered to, or supported, these cultural traditions.
presumption of accommodating local cultural values, results in ethical relativism that may lead to widespread exploitation of (vulnerable) populations.\textsuperscript{269}

Conversely, the defenders pointed out that collaboration in international clinical research requires respecting local values and custom, as well as guidelines of local IRBs for reviewing research protocols. Indeed, Varmus and Satcher appealed to the support that the trials obtained from officials in the host countries who denounced the criticism.\textsuperscript{270} Yet, Angell notes that IRB study approval is “highly variable in its responsiveness to patients’ interests when they conflict with the interests of researchers.”\textsuperscript{271}

Moreover, “the asymmetry in knowledge and authority between researchers and their subjects” often leads to informed consent processes that do not afford real or adequate protection to prospective subjects.\textsuperscript{272} In any case, both the issues of (local) IRB approval and informed consent can be seen—and were presented by the studies’ defenders—as primarily matters of legitimate cultural difference, thus giving rise to discussions about the need to find a golden ethical mean in international collaborative research: one that would combine respect for cultural identity, individual autonomy, and a high ethical research standard.

This series of trials brought to the fore numerous ethical issues (e.g. exploitation of vulnerable subjects, deception, undue harm and risk, unavailability of treatments, etc.) that have plagued other clinical trials, and for this reason they can be seen as a case study of clinical

\textsuperscript{269} Angell 848

\textsuperscript{270} Varmus and Satcher mentioned the supportive letter of Edward K. Mbidde, chairman of the AIDS Research Committee of the Uganda Cancer Institute, who pointed out that “it is not NIH conducting the studies in Uganda but Ugandans conducting their study on their people for the good of their people.” Varmus and Satcher 1005

\textsuperscript{271} Angell 847

\textsuperscript{272} Ibid.
research in general. They were also remarkable for being the object of contention between groups of people who appealed to the same principles of the bioethical framework we examined earlier to make their ethical judgments and construct their respective arguments.

Looking back at these arguments, I believe that the defenders’ support of the equipoise option should not be easily dismissed. Lack of previous data about how the standard ACTG 076 regimen would fare for the particular populations of subjects in sub-Saharan Africa may justify the placebo design, given that there is parallel endemicity of other diseases that can compromise the safety and efficacy of the experimental therapy. However, certain of these trials could have been designed as equivalence studies to enlarge the range of comparison between all possible treatments.

Moreover, HIV infection and AIDS are not the only grave public health problems in developing countries, whereby large segments of the population must bear other formidable challenges (besides endemic diseases), such as chronic malnutrition and lack of clean water. In the circumstances, governments may well choose to purchase second-tier treatments that are more affordable in the interests of providing at least a respectable minimum of health care, while they make additional cost-effective investments in the areas of nutrition, water improvement, and education.

On the other hand, the critics rightly pointed in the direction of the economic reasons that prompted these trials, although a research hypothesis (in a strictly scientific sense) cannot possibly contain an economic component, as had been their recommendation. However, the crux of the matter is to examine the problem of the unavailability of important treatments—and often the complete lack of health care—that plagues sizable populations in large parts of the world. Remarkably, the critics of the studies did not go far enough in asking this hard question (at least
in the context of critiquing these trials), perhaps because they felt they had to focus on the
narrow ethical problems presented by the procedural handling of the research. Looking back at
the four principles we examined, which were taken into account in both critiquing and defending
the studies, we realize that their framework can only offer a limited ethical analysis of research,
and only in reference to the micromanagement of its internal processes.

However, unless these trials are seen beyond their mere technical procedures and narrow
ethical reasoning, and within the larger spectrum of their social, economic, and political
parameters, we cannot obtain sufficient understanding of their broader social and moral
ramifications. This larger context should allow us to reflect on what is beneficial and just for
people, and imagine what can change their life conditions from bare survival to a flourishing
type of existence, at least at a level that is minimal but sufficient to make a difference.

The “human capabilities” model: suggesting a different ethical perspective

A universalist type of response to the need for human flourishing has been advanced by
Martha Nussbaum in her “capabilities approach” to the politics and ethics of development.273
Initially pioneered by Amartya Sen, the notion of human capabilities carves out a space whereby
standards of living can be compared, and people’s quality of life evaluated in terms of what
people can actually be and do. As a conception of economic comparisons, this approach stands
in opposition to using conventional indicators such as GNP (or per capita income), which point
to an average (but largely fictitious) level of people’s economic assets.274

To be sure, economic questions pertaining to people’s life situations (whether in
employment, education, health care, or even, clinical research) are paramount in this approach,
as they point to the material conditions on which people’s circumstances are contingent. Indeed, Nussbaum takes a Marxian stance toward human life in stating that “the major powers of a human being need material support and cannot be what they are without it.”

Yet, Nussbaum’s theory of human capabilities diverges from Sen’s primarily in three ways: First, she upholds a feminist position on the question of social equality, but one that is radically different from that of postmodern feminisms, in the fact that hers makes an appeal to universal, cross-cultural notions of human dignity. Indeed, Nussbaum rejects the sort of feminism that rests on notions of cultural relativism as a theoretical approach to human development and justice. Although she expects Sen to agree on the value she places on universal norms, he may not altogether endorse all of her arguments against relativism.

Secondly, Nussbaum relies considerably on, and explicitly appeals to, Aristotle and Marx’s notion of what functions are “particularly central in human life, in the sense that their presence or absence is typically understood to be a mark of the presence or absence of human life.” Thus, the intrinsically human, rather than simply animal, character of such “core” areas of functioning plays an important role in defining Nussbaum’s conception of human capabilities, a number of which are held as central for human life, although this philosophical justification is not evident in Sen’s approach.

\[275\] Ibid. 73
\[276\] Ibid. 7-8, 11
\[277\] Ibid. 13
\[278\] Ibid. 71-2
\[279\] Ibid. 13
Thirdly, Nussbaum proposes these central capabilities as a set of basic political principles to be adopted as constitutional liberties, and hence citizens’ rights, requiring the commitment of governments to actively safeguard and bring them to fruition for the flourishing of each and every person. The fact that these liberties/capabilities allow people to achieve what they are able to be and do can be consistent, in Nussbaum, with differing accounts of distribution of social and material resources. This feature, according to Nussbaum, makes it possible to argue for a constitutional endorsement of at least a certain threshold in these liberties. Neither the idea of the political endorsement of these capabilities, nor the suggestion of the threshold as a theoretical point, is present in Sen.

Nussbaum argues that the human functional capabilities are all fundamental for a person’s wellbeing and opportunities to flourish, but they are systemically violated for many in the world, typically in the sense that the social and political institutions that could sustain and promote them are not protected. These central capabilities are those of life, bodily health and integrity, the ability to use one’s senses, imagination, practical reason, and emotions freely, the possibility of affiliation without fear (including freedom of assembly, political speech, or any social interaction), the possibility of living with concern for and in relation to other biological species (i.e. animals, plants, etc.), the freedom to play, laugh, and enjoy recreational activities, and the possibility of being in control of one’s political and material environment (including the right of political participation, owning property, and employment on an equal basis with others).

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280 Ibid. 74
281 Ibid. 12-3
282 For the list and discussion of this model’s human capabilities, see Nussbaum 78-86.
Located in the philosophical tradition of political liberalism, Nussbaum’s model of human capabilities is not a complete theory of justice, but promotes a conception of equal citizenship regardless of individual differences in gender, race, ethnicity, social and economic class, and the like. Justice is grounded precisely in the notion, and reality, of equal citizenship, which cannot be accomplished unless (at least) a threshold of liberty in achieving these human capabilities is respected politically, and systematically delivered to citizens to sustain core areas of their human functioning.

Neither this threshold, nor any of the capabilities, is negotiable, because their absence would violate the practical sustenance of these functions, and would (theoretically) counteract the inviolability of the human person. This condition requires that human capabilities not be overridden by demands of social welfare advanced on utilitarian grounds. The conceptual basis of individual inviolability (indeed, of the entire capabilities normative model) is an intuitive notion of human dignity, whose content lies in the “human powers of practical reason and sociability.” These powers essentially speak to the ability of the human person to shape his/her own life as a free being, and “in cooperation and reciprocity with others.”

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283 Nussbaum uses this term as it has been established by John Rawls. Ibid. 5, 59; Rawls 71

284 Nussbaum 71

285 The Kantian idea of human inviolability states that persons must be treated as ends in themselves, and not as mere means serving given ends. It is both an ontological and moral idea. Ibid. 73; 190n

286 In this regard, the human capabilities approach is very much in tune with the principles of respect for autonomy and justice in the principlist bioethical model. Indeed, the latter is likewise rooted in the liberal tradition.

287 Ibid. 72

288 Ibid.
Nussbaum’s model, in its normative, ethical, and political dimensions, creates certain demands of distributive justice and individual entitlements on account of persons’ inviolable dignity and intrinsic human functioning. The right of each and every person to (at least) a threshold level of material and social resources should afford them the opportunity to see their capabilities flourish. This threshold, according to the model, should be the guiding light in the structuring of political and social institutions (hence the proposal of these capabilities/principles as minimal political goods).\(^{289}\)

Institutional (re-)structuring, at or above the threshold, has particular significance when concerning the weakest members of society; that is, those with unequal economic status and social worth. Thus, the question of socio-economic inequality becomes paramount in Nussbaum’s feminist approach to human capabilities, especially with regard to the politics and ethics of development.\(^{290}\) This is so because the issue of social inequality is most visible in the Third world, where the case of women’s low social status exemplifies the most acute form of failing these human capabilities. At the same time, Nussbaum argues, women in developing nations provide the most visible test of how problems of justice can be addressed satisfactorily when the human capabilities are advanced and protected.

In her ethnographic narrative\(^{291}\) about women’s lives in Kerala (the poorest region in India), Nussbaum recounts the disastrous implications that culturally shaped preconceptions of

\(^{289}\) Ibid. 75

\(^{290}\) The term has a successful double connotation in this model: human development (for all people) in the area of capabilities, and development of Third world economies through a focus on the political advance of women’s capabilities.

\(^{291}\) Nussbaum adopts an empirical approach in grounding her case by reflecting the cross-cultural/universal character of her theory on phenomenological particulars she discovers on the field.
female inferiority have on persons because of their being female. Not only are women deprived of resources as basic as adequate nutrition and health care, but of substantial opportunities for formal education and the acquisition of professional skills that could ensure them social and economic independence. Moreover, conditions of chronic poverty exacerbate, and are exacerbated by, these gender-related deprivations in a vicious cycle.

On the other hand, Nussbaum also explains the liberating and flourishing outcomes, for women, of policies that allow adequate—although threshold-level—structural changes toward women’s social development through education and economic empowerment. Such policies embody the idea of constitutionally protecting, and actively promoting, the human capabilities against the power of culturally shaped attitudes of social exclusion. Lastly, Nussbaum holds that considerations of justice for women have been disproportionately silenced in debates about international development, and should become the central focus of a project aimed at constructing basic political goals for all persons, irrespective of differences in gender, race, socio-economic class, ethnicity, and national origin.

Alternative questions of justice and autonomy in the ACTG 076 trials: the significance of the human capabilities model

Nussbaum’s normative framework does not explicitly address issues of justice in transnational clinical trials, but, if applied on the ethical assessment of such research, it can have significant theoretical and practical import. Before revisiting the ACTG 076 trials in sub-Saharan Africa, in order to interpret them from the human capabilities perspective, we should

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292 Nussbaum’s narrative of women’s predicament is valuable in showing graphically that capabilities (and their lack) are tightly connected with the social (and not an essentialist) situation of each person.
take a look at the theoretical grounds on which we may choose to adopt an alternative approach to the bioethical one in examining ethical questions of (transnational) research.

In the second chapter, the analysis of the nature of scientific theories, and particularly of the ways in which scientific beliefs are shaped by social values, has shown that these beliefs are the outcome of socially constructed meanings and significations. We have also seen that mutable socio-cultural constructs of health, disease, and human wellbeing/body form the conceptual foundations of the structures of clinical research and its ethical reasoning. It is, thus, reasonable to argue that moral beliefs about clinical research are unfixed and unstable, and equally shaped by social values in the way scientific beliefs were shown to be. This must be particularly true of the principlist bioethical model, which is claimed to be rooted in common morality; that is, commonly-held beliefs.

Moreover, we have seen that, unless the bioethical principles (themselves beliefs) are specified and contextualized, they do not acquire meaningful content. Yet, their specification within certain contexts, as well as their balancing against each other, require the use of values that can be different each time the principles are specified and balanced by different actors. Indeed, the critics and supporters of the ACTG 076 transnational trials interpreted the same bioethical principles differently in an effort to represent the reality of the same phenomena in a different light. In fact, the principlist bioethical model allows for such breadth of interpretation. Therefore, we can justifiably rely on different values (say, the human capabilities) to achieve a different understanding and ethical evaluation of clinical research.

Additionally, it is good to remember that the ACTG 076 trials in sub-Saharan Africa were partly justified on the grounds that the lack of treatments, and the unfeasibility of expensive ones, necessitated the onset of this particular research. However, this reasoning questions neither
the causes of this lack of resources, nor the ethics of these causes. It simply accepts them as part of a *status quo*, and then proceeds to do its ethical analysis, which is of limited scope. In the case of sub-Saharan Africa, this *status quo* is largely punctuated by specific facts: a globalized neo-liberal economics—a sort of contemporary colonialism—that depletes the continent’s resources, pervasive corruption of national governments that further deprives populations of vital assets, quasi-perpetual warfare and population displacement, and abject chronic poverty, malnutrition, and disease.

For all these reasons, a different ethical evaluation of the ACTG 076 trials can emerge, if we choose to assess them, not as an isolated scientific venture in the midst of unfortunate contingencies, but as tightly connected to these contingencies. In this regard, Nussbaum’s human capabilities model can offer a broader, more penetrating moral evaluation of this research, and inclusive of the socio-economic features that have shaped it. This is so because the model’s values are precisely about the material dimension of what people can be and do in various domains of life, including that of medicine and health care, which allows them a certain handling of their health situation.

Of course, the Western sponsors of the trials, and local IRBs, had indeed taken socio-economic factors (i.e. disease, state of local economies, etc.) into account in justifying their research design. However, the idea for applying Nussbaum’s model is about critically questioning these factors (as the supporters of the trials did not), with the view of finding whether some of the internal processes of this research were the result of, and indeed fed on, the aforesaid external contingencies.

The major question that the human capabilities approach would ask is whether at least a threshold of material resources in the areas of health care, public health, and the protection of
pregnancy and child birth was available to citizens.\textsuperscript{293} In the sub-Saharan African context of a rampant epidemic as devastating as AIDS, and of desperate need for health care, HIV-positive women did not seem to have many options, other than enrolling in clinical research, to protect their infants from HIV infection.\textsuperscript{294}

Indeed, the ACTG 076 trials were notable in that they involved thousands of women and their fetuses, both of which may be said to constitute a tremendously vulnerable group. In their case, any one of the qualifications of vulnerability (as defined by the international research guidelines\textsuperscript{295}) obtained, and certainly the condition related to the non-availability of necessary treatments in some of the world’s poorest areas. In these parts of the world, core areas of human functioning are, for many, suppressed and reduced to no more than bare survival, whose material support is curtailed even to the level of adequate nutrition and clean water.

Based on the recognition that the capability of \textit{bodily health} had been failed at the level of available material resources in the communities hosting the ACTG 076 trials, the principle of respect for autonomy should receive a new contextualization. Typically, the autonomy of research subjects is evaluated in terms of the informed consent process, as a way of ensuring

\textsuperscript{293} Nussbaum’s capability/principle of \textit{bodily health} explicitly endorses the definition of reproductive health established in the 1994 International Conference on Population and Development, which requires that “every sex act should be free of...infection” and “every birth should be healthy.” Nussbaum 78

\textsuperscript{294} This clearly parallels the case of AIDS patients in the 1980s, demanding, through their advocacy groups, freer access to clinical research and its potential benefits, as well as more federal research funding.

\textsuperscript{295} “Vulnerability refers to a substantial incapacity to protect one's own interests owing to such impediments as lack of capability to give informed consent, lack of alternative means of obtaining medical care or other expensive necessities, or being a junior or subordinate member of a hierarchical group.” The Council for International Organizations of Medical Sciences (CIOMS - 2002)
persons’ freedom to make medical decisions. However, if autonomy is the expression of persons’ possibility to make personal choices according to their values, the concept has no practical import unless people have real options available to them.

This possibility (or capability) is contingent on their being unconstrained from external contingencies/pressures, such as authority or dire need for basic resources. In the case of the ACTG 076 trials, subjects’ enrollment seems to have been almost “coercive” due to the contingencies of poverty and social unresponsiveness to disease, which researchers may well have exploited to recruit subjects (although probably not guilty of procedural coercion). In this regard, their obligation to respect subject autonomy cannot be seen as fulfilled, even if we assume that the consent process was technically proper (although testimonies, in certain instances, pointed to the opposite).

Therefore, autonomy was greatly compromised by people’s initial decisions to join the trials out of dire necessity. To avoid rendering autonomy a cosmetic feature in research ethics, the capabilities model would require that clinical research be part of a larger social institution of health care that can systematically deliver to people legitimate and meaningful alternatives to research. Such material conditions would ensure the presence of appropriate medical infrastructure for diagnostic and therapeutic practices, in which the best-proven treatments worldwide would also be applied for the benefit of Third world patients. Indeed, the universal character of Nussbaum’s model would reject the application of a different, second-tier therapy for women in sub-Saharan Africa, or its testing against placebo in an equipoise-designed trial, when a standard treatment already exists.

Nussbaum’s normative model also has implications for the meaning of justice in the ACTG 076 trials. In the four-principle bioethical model, we have seen how the distinction
between health care and clinical research becomes blurred, and produces a notion of research justice that is, more or less, seen as distributive justice in the allocation of scarce health care resources. The case of this transnational research greatly exemplifies this tendency, as subjects surely used it as a badly needed health care opportunity. Yet, this points to a radical difference in the research expectations between investigators and subjects.

We have seen as well that fairness in patients’ “access to research benefits” is ensured by the scientific validity of the screening process for subject inclusion. This (procedural) condition of justice may well have been satisfied in these trials, yet, the subjects’ and investigators’ radically different positions toward this research was enough to compromise justice, at least as seen from the subjects’ perspective, and especially in relation to the lack of therapeutic benefit for control subjects (this was a placebo-controlled equipoise set of studies).

As in the case of autonomy, research justice does not occur in a social vacuum, independent of what people may (or may not) access outside of the research setting. This is not to say that people’s decisions to enroll in a trial out of sheer need for health care necessarily results in their exploitation, but it does not exclude this possibility either. To ensure justice in research, the human capabilities model would require the material support of people’s right to health care resources, at least at an adequate minimum. This right would have to be constitutionally protected, and structurally guaranteed to all citizens, including women and other (vulnerable) minority groups.

In the context of the ACTG 076 trials, the absence of a realistic plan for the future delivery of the tested therapy—if proven effective—to the wider relevant population, from which the research subjects were recruited, would be unacceptable by the ethical standards of the

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296 According to the new paradigm that views justice in clinical research in terms of fairness in
human capabilities model, especially because these trials had been justified primarily on the basis of the state of economy in the hosting countries. It is ironic that the use of “collaborative research” is favored in circles sponsoring research in the Third world, but the term may not be more than a euphemistic device, concealing the fact that many “collaborative” trials cannot be implemented in the West for ethical reasons.

Nussbaum’s model would rather favor a collaborative international effort to forgive Third world debt to industrialized nations, and provide sub-Saharan Africa with appropriate aid, and not temporary charitable relief. Such aid should be channeled into appropriate social sectors to generate possibilities of real development in the area of education and professional training that could promote people’s—and especially, women’s—economic and social independence. It would also be used for the development of national infrastructure to meet the basic needs of human functioning.

This has been a preliminary account of the theoretical and practical implications of the human capabilities approach, in Martha Nussbaum’s version, on the ACTG 076 transnational clinical trials. My aim was to use it in the way of suggesting how it is possible to affect autonomy and justice in clinical research, as well as in health care policy, as the capabilities model advocates a structural and institutional approach to justice. Such a normative and political program can have important ramifications on the ethics and practice of transnational clinical research, which should be seen as part of a truly collaborative international effort toward the economic and social development of Third world populations.

Therefore, in my exploration of the various aspects of clinical research, and especially that of justice, it is a biopolitical, rather than a strictly bioethical, perspective that I have sought.

patients’ “access to research benefits.” Ch. 3 93-5
to underscore. If the bioethical model is not inspired by a broader social and political perspective, it can only limit itself to generating guidelines and recommendations that are always easy to breach, or at least, interpret in ways that do not really serve the model’s principles. In closing, I would like to advance the idea that the ramifications of a normative model such as the one based on the human capabilities are worth exploring in the context of bioethics, both as concerns the ethics of health care as well as clinical research.
AFTERWORD

This thesis has examined the various social, conceptual, and ethical aspects of clinical research involving human subjects. The conceptual basis of research was explored, both in its socio-cultural and scientific dimensions, with an explanation of the methodologies used in current randomized clinical trials. Throughout this work, several instances of research in the history of medicine, exhibiting morally questionable treatment of subjects, were discussed with respect to specific ethical problems that they posed. The dominant bioethical framework known as principlism, which is used for the ethical assessment of research practices, was explicated in terms of how it responds to fundamental ethical problems of research.

This work has paid particular attention to transnational clinical trials, sponsored by Western research institutions, and typically carried out in resource-poor nations of the Third world. Among them, the ACTG 076 HIV/AIDS trials, conducted in sub-Saharan Africa, were discussed as a case study of ethical evaluation of transnational clinical research. Finally, a specific model of distributive justice, advanced by Martha Nussbaum and based on the human capabilities approach, was proposed as an alternative normative framework to the principlist bioethical model for the evaluation of transnational clinical research.

This thesis ends with the recommendation that the normative implications of the human capabilities approach on clinical research be further investigated as possible steps of a future health policy. One of the model’s strengths is that it addresses the injustice of gender-based inequalities, and their adverse effects on individuals and societies, especially in a context of deep systemic poverty. If applied in the context of Third world development, and appropriately interpreted to fit the transnational research culture and setting, this model can contribute to
changing the broader, socio-structural environment of research towards a more equitable and fair
distribution of health resources.

Such an environment, modified by the human capabilities model, will have to ensure an
immediate and universal scaling-up of anti-retroviral treatments, which have been largely
unavailable to people so far (with, obviously, a reduction in prices by Western pharmaceuticals).
It will also include the political will by national governments to empower women, and HIV-
positive people in general, through the creation of a new culture of openness that will be free of
social stigma, so as to enable patients to stick with therapies.

This empowerment could be furthered by the proactive training of HIV/AIDS patients,
and women in particular, as part of a national workforce that can strive to enhance other patients’
adherence to treatments. Well-known shortages in human resources in the Third world, due to
increased, AIDS-related death rates, can be addressed rapidly and effectively in part through this
strategy, if people are cared for. The effort of empowerment must be a sustained political
commitment, and may include the monitoring and evaluation of health programs, both in health
care and clinical research, by HIV-positive persons. People’s experience with HIV can, thus,
become a source of insight for creating effective therapeutic regimens for the needs of specific
populations.

Lastly, this culture of openness and individual empowerment will require an authentic
practice of informed consent in clinical trials, respectful of individual autonomy. This autonomy
can be affirmed, and further cultivated, if people can make conscious choices to enroll trials,
when they already have the opportunity for treatment as health care. Such strategies can be
crucial in effectively addressing the AIDS epidemic in the Third world, and at the same time
ensure the halting of the disease worldwide. For this reason, the human capabilities approach is
worth examining as a possible contributor to policy for health care and international clinical research programs.
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